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THE MEDICAL JOURNAL OF AUSTRALIA

VOL. I.—16TH YEAR. SYDNEY, SATURDAY, JUNE 8, 1929. No. 23.

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VOL. I.—16TH YEAR. SYDNEY, SATURDAY, JUNE 8, 1929. No. 23.

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Symposium on Snake Bite.

OBSERVATIONS ON THE CERTAINLY LETHAL DOSE OF THE VENOM OF THE DEATH ADDER (*ANCANTHOPHIS ANTARCTICUS*) FOR THE COMMON LABORATORY ANIMALS.[1]

By C. H. KELLAWAY, M.C., M.D., M.S., M.R.C.P.
(From the Walter and Eliza Hall Institute, Melbourne.)

EXCEPT for the approximate value of the certainly lethal dose by subcutaneous injection in the rabbit,[1][2] there was prior to Fairley's recent work on sheep[3] no exact information concerning the toxicity of this venom. In the present paper there are recorded a few observations on the effects of the venom in horses, monkeys and cats and more numerous ones on rabbits, guinea-pigs, rats and mice.

The rabbits, guinea-pigs, rats and mice were of the same stocks as those used for the determination of the certainly lethal dose of the venoms of the tiger snake,[4] copper-head[5] and of *Pseudechis guttatus*.[6] As far as possible the weights in each group have been uniform and the weighings have been made in the early morning before the animals were fed. The venom used was carefully dried and great care was taken to insure its being unmixed with that of any other species.

EFFECTS IN THE HORSE.

The injections were made subcutaneously into the tissues at the side of the neck. The venom was used in a concentration of ten milligrammes per cubic centimetre for the first and third animals in the table and of four milligrammes per cubic centimetre for the remainder. The results are set out in Table I.

TABLE I.
Results of Subcutaneous Injection in Horses.

Sex.	Weight in Kilograms.	Dose in Milligramme per Kilogram.	Results.
Male gelding	203	0·05	Died in 8 hours.
Female ..	251·4	0·04	Paralysed in 7 hours 10 minutes and died in 15 hours.
Male gelding	330	0·04	Died in 52 hours.
Male gelding	554	0·02	No symptoms apart from blood-stained urine and local swelling at the site of injection.
Male gelding	330	0·01	No symptoms apart from slightly blood-stained urine and swelling at the site of injection.

These observations are too few in number to do more than indicate the degree of toxicity of the venom for the horse. The certainly lethal dose is of the order of 0·04 milligramme per kilogram.

The Symptoms.

The two animals which received 0·01 and 0·02 milligramme per kilogram, had slight swellings at the site of injection which disappeared within forty-eight hours. That which received the larger dose, passed blood-stained urine for twenty-four hours and in the other horse the urine was less darkly stained for a shorter period. This last animal was reinjected with 0·04 milligramme eight days later. In all the animals red blood cells and pigment were present in the urine and after the larger doses, 0·04 and 0·05 milligramme per kilogram, the urine in the bladder at death was thick and tarry. This almost black urine contained enormous numbers of red blood corpuscles. The horse which received 0·05 milligramme per kilogram, exhibited no symptoms until about an hour before death. It then developed paralysis of the tongue and lips. It "went down" ten minutes before death. The second animal in the table "went down" seven hours and ten minutes after the injection and after twelve hours showed definite paralysis of the limbs. It died in convulsions fifteen hours after injection, but unfortunately the symptoms were not very closely observed.

The third animal had had a small dose of venom eight days earlier. At no stage in its illness after injection with a larger dose was paralysis of the limbs obvious. Ten hours after the injection the tongue and the muscles of the lips were paralysed. There was salivation, but no sweating. The urine was blood stained. The head could not be held up, the pupils were contracted and there was some general bodily weakness. After twenty-two hours, in addition to the paralysis of the tongue and lips, there was definite though slight respiratory embarrassment and some patchy diaphoresis. By forty-eight hours the breathing had become definitely laboured and the *alæ nasi* were twitching spasmodically with each respiration. The animal "went down" finally forty-seven hours after the injection and died quietly five hours later.

Post Mortem Findings.

The findings in the three animals which died were strikingly uniform. At autopsy four to eight hours after death the blood was found clotted in the heart and great vessels. There was blood-stained fluid in the pericardium and many petechial hæmorrhages were present in the pericardial fat and in the endocardium. The interior of the large vessels was stained with blood pigment. The lungs showed intense hæmorrhagic œdema with patchy areas of massive hæmorrhage and there were many petechial hæmorrhages in the bronchial mucosa. The bronchi contained yellow-stained frothy secretion. The spleen had a black currant jam appearance similar to that seen following death from tiger snake venom and there were many small subcapsular hæmorrhages. The kidneys in one horse were intensely hæmorrhagic with evidence of hæmolysis. In the other two animals there were streaky hæmorrhages throughout the cortex and medulla. The urine in the bladder was black and of the consistence of tar and contained red blood corpuscles and much altered blood pigment. There were only a few petechiæ on the mucosa of the bladder. In the

[1] This research was carried out under a grant from the Department of Health of the Commonwealth Government.

adrenals in one animal there were many small hæmorrhages both on the surface and scattered through the cortex and medulla. There were hæmorrhages and hæmolysis all along the attachment of the mesentery to the small bowel. In the mare the uterine mucosa was congested. The surface of the brain was also congested and there was faintly blood-stained fluid in the ventricles. At the site of injection there were hæmorrhagic œdema and congestion spreading for a considerable distance in the subcutaneous tissues of the side of the neck.

EFFECTS IN THE MONKEY.

A few monkeys (*Macacus rhesus*) received the venom subcutaneously in the forearm in a concentration of 2·0 milligrammes per cubic centimetre. The results of injection are shown in Table II.

TABLE II.

Results of Subcutaneous Injection in Monkeys.

Weight in Kilograms.	Dose in Milligramme per Kilogram.	Death Times.
4·69	0·2	Died in 2 hours 45 minutes.
2·63	0·2	Died in 4 hours 50 minutes.
2·7	0·15	Died in 3 hours 50 minutes.
4·03	0·1	Moderate symptoms, recovered by third day.
2·95	0·05	Slight symptoms, recovery after 24 hours.
2·73	0·02	No symptoms.

The last two animals received their dose in a concentration of 0·1 milligramme per cubic centimetre. The number of observations is too few for the estimation of the certainly lethal dose, but the results indicate that it is not far removed from 0·15 milligramme per kilogram.

The Symptoms.

The symptoms presented by these animals were very striking. With 0·05 milligramme per kilogram the only sign observed was slight bilateral ptosis. With 0·1 milligramme per kilogram there was obvious ptosis within four and a half hours. After twenty-two hours there was ataxia and slight weakness in all movements. The animal sat with bowed head clinging to the walls of the cage for support. There was a discharge from the nose and the mouth remained open. There was definite respiratory distress. During the second day there was muscular weakness and the animal was unable to eat food presented to it; slight dyspnœa was still present at the thirty-fifth hour. By the forty-eighth hour recovery had commenced and rapidly progressed.

The monkey which received 0·15 milligramme per kilogram, developed ptosis within two hours. He shortly became dyspnœic and after two and a half hours was sitting upright clinging to the walls of the cage for support, the head falling forward on his breast. He was somewhat dyspnœic and definitely cyanosed. After three hours and forty minutes respiration failed. He became deeply cyanosed with ineffective action of the accessory muscles of respiration. The pupils dilated and there were a few twitching semiconvulsive movements of the limbs. He fell down on the floor of the cage apparently dead, but the heart went on beating strongly for some minutes.

The animals which received larger doses also died with respiratory failure, but without convulsions.

Post Mortem Findings.

There was no local lesion at the site of injection. The blood was fluid and no clots were found anywhere. In two animals the heart was still beating when the autopsy was performed. The clotting times of blood taken from the heart immediately after death were five, seven and a half, and two minutes. In the animal which received 0·15 milligramme per kilogram, the phrenic nerves stimulated immediately after death were sensitive and good contraction of the diaphragm was obtained. In one monkey which received 0·2 milligramme, the right phrenic nerve was insensitive and stimulation of the left phrenic nerve caused only a feeble diaphragmatic contraction. There were no obvious lesions in any of the organs at autopsy. The lungs, trachea and bronchi were not congested.

Death in this species appears to result from the neurotoxic properties of the venom and is preceded by failure of respiration. The lung lesions so characteristic in other species were not evident, but death may have occurred too early to allow of their development.

EFFECTS IN THE CAT.

The effects of subcutaneous injection of venom in the flank was studied in a few cats. The venom was administered in a concentration of two milligrammes per cubic centimetre. The result is seen in Table III.

TABLE III.

Results of Subcutaneous Injection in Cats.

Sex.	Weight in Kilograms.	Dose in Milligrammes per Kilogram.	Death Times.
Female ..	2·75	1·5	Died in between 2 and 4 hours.
Male ..	3·47	1·2	Died in between 2 and 4 hours.
Female ..	3·00	1·0	Died in between 2 and 4 hours.
Male ..	3·40	0·8	Died in between 2 and 4 hours.
Male ..	2·65	0·6	Died in 2 hours 20 minutes.
Female ..	2·67	0·6	Died in 3 hours.
Female ..	1·1	0·5	Died in between 7 and 17 hours.
Male ..	2·15	0·5	Died on fifth day.
Female ..	2·2	0·3	Moderate symptoms, recovered on second day.

The number of animals is insufficient for the determination of the certainly lethal dose, but this is evidently not far removed from 0·5 milligramme per kilogram. As with other elapine venoms the cat is definitely more resistant than the other species examined.

The symptoms produced by injection in this species were those characteristic for this venom in most others. In the early period following the injection they were predominantly respiratory. There was sometimes obstructive cough. Excessive secre-

tion of tears was noted in one animal, but in all there was some dribbling of secretion from the mouth and frequently a discharge from the nostrils. There was moderate dyspnœa and the breathing was audible, the fremitus from wet *râles* being felt through the chest wall. Paralysis appeared later and, as is usual with elapine venoms, was noted first in the hind limbs. Its earliest manifestation was a weak ataxic gait. Later still the fore limbs and neck muscles were involved. Death occurred quietly without convulsions. The animal which received the smallest dose presented respiratory symptoms only and had completely recovered by the second day. One cat which received 0·5 milligramme per kilogram was paralysed in the hind and fore limbs after twenty-four hours. There was extreme weakness of the neck muscles and the pupils were contracted. By the third day it had apparently recovered, but died quietly two days later.

Post Mortem Findings.

Except for a minute hæmorrhage in one animal there was no obvious local lesion at the site of injection. The lungs in all were intensely congested and œdematous, with a few massive or numerous petechial hæmorrhages. In two cats there were multiple petechial hæmorrhages in the spleen. The clotting time of the blood removed from the heart immediately after death was normal (four to five and a half minutes). There were no other obvious lesions and hæmoglobinuria was not observed, though possibly its absence may have been related to the short duration of illness with this range of dosage.

THE EFFECTS IN THE RABBIT.

The Effects of Intravenous Injection.

The result of the intravenous injection of the venom in a concentration of 0·4 milligramme per cubic centimetre into a marginal vein of the ear of rabbits is set out in Table IV.

TABLE IV.

Results of Intravenous Injection in Rabbits.

Number of Animals.	Average Weight in Kilograms.	Dose in Milligramme per Kilogram.	Results
1	1·57	0·4	Death in 28 minutes.
2	1·42	0·15	One died in 1 hour 24 minutes and one in 2 hours 7 minutes.
7	1·50	0·12	One died in 1 hour 35 minutes, one in 2 hours 10 minutes, two in 3 hours 10 minutes, one in 4 hours, one between 3 and 5 hours, and one in less than 20 hours.
2	1·64	0·10	No symptoms.

The certainly lethal dose by this route is 0·12 milligramme per kilogram for rabbits between 1·2 and 1·7 kilograms.

The Symptoms.

With the largest dose the animal was obviously affected after about ten minutes. It squatted with its hind quarters raised and its head down on the floor lying tonelessly on one side. Shortly afterwards the animal fell over and lay on one side in a condition of collapse with the limbs thrust out. There was general quiet paralysis with incomplete loss of tone. Starting movements were absent. Death occurred from respiratory failure. With smaller doses and death in from one to four hours the symptoms were somewhat different. The hair round the mouth and nose was wet and there was noisy, audible breathing suggesting the presence of œdema of the lung, long before any collapse or paresis was noted. A short time before death the animal was collapsed and death occurred suddenly, in some cases with obvious cardiac failure.

Post Mortem Findings.

In the animal which died in twenty-eight minutes, the heart was found beating strongly after death. The spleen was enlarged and the intestines somewhat congested. The blood was everywhere fluid and the clotting time was five and a half minutes. There were a few small hæmorrhages in the mesentery, but no other obvious lesions. In animals dying in from one to five hours, the lungs were distended, congested and œdematous. The lungs filled the thoracic cavity when the chest was opened and were distended partly with air and partly with fluid. There were a few petechial hæmorrhages scattered through them. In several animals there were petechial hæmorrhages in the thymus. Occasionally, but not regularly, there was excess of bile in the small intestine and in one animal the small intestine was slightly congested and there was free fluid in the peritoneal cavity. The blood in the heart and great vessels was fluid and the clotting times were within normal limits (three and a half, five, five and a half, six and six and a half minutes).

In the animal which died in between eight and twenty hours, there were large areas of collapse in the lungs, the surrounding tissues being distended and œdematous.

The Effect of Subcutaneous Injections.

The results of subcutaneous injections are recorded in Table V. The sexes of the animals used were evenly distributed and their weights ranged

TABLE V.

Results of Subcutaneous Injection in Rabbits.

Number of Animals.	Average Weight in Kilograms.	Dose in Milligramme per Kilogram.	Results.
8	1·45	0·16	One died in 3¾ hours, one between 4 and 6 hours, one in 8 hours, one in 8 hours 40 minutes, and four in less than 19 hours.
6	1·5	0·15	One died in 4 hours, one in 4¼ hours, three in less than 19 hours, and one on the second day.
4	1·5	0·14	Two died in between 5 and 8 hours, one between 10 and 20 hours, and one survived.
4	1·59	0·13	One died in 3 hours 55 minutes, one in 4 hours 3 minutes, one in 8 hours 50 minutes, and one survived.

between 1·17 kilograms and 1·76 kilograms, all except six being between 1·4 and 1·6 kilograms. The venom was administered in a concentration of 0·4 milligramme per cubic centimetre.

The certainly lethal dose by the subcutaneous route is 0·15 milligramme per kilogram for rabbits between 1·3 and 1·7 kilograms. This is lower than the approximate figure 0·2 milligramme per kilogram given by Tidswell[2] and by Lamb and Martin.[1] The subcutaneous intravenous index is 1·25.

The Symptoms.

The symptoms exhibited by animals injected with doses of this order and dying within nineteen hours were very uniform. Within four hours of the injection the hair round the nose and mouth was obviously wet and the breathing was audible and somewhat laboured, the clinical picture suggesting œdema of the lung. At this stage there was neither collapse nor paralysis. Four hours later paralysis was still absent in many animals, though in a few there were paresis and ataxia. At this stage the posture was characteristic, the head lying on one side on the floor of the cage and the hind quarters being hunched up. Later collapse and paralysis were both evident, the animal lying on its side with feeble respirations, but no starting movements. Animals dying before the eighth or ninth hour were under observation for the whole period between injection and death. In these the onset of paralysis was at about the seventh or eighth hour, the early symptoms being those detailed above. The animals were completely paralysed only a short time before death, which took place by respiratory failure. A final convulsive seizure, which was very greatly modified by the extent of the paralysis, signalized in a few animals the failure of respiration and terminal asphyxia. The pupils were dilated about two-thirds of their maximal extent throughout the illness and sometimes became more dilated terminally. The pupil reflex was lost shortly before death, which occurred quite suddenly.

Post Mortem Findings.

The blood was fluid in all the animals examined immediately after death and in those examined some time later when the animals were in rigor, no evidence of *ante mortem* clotting was found. The clotting time was normal or slightly delayed (three, seven and eight minutes). When the autopsy was performed immediately after death, the heart was frequently found beating and stimulation of the phrenic nerves caused brisk contraction of the diaphragm. At the site of the injection there was some œdema and occasionally a small zone of hæmorrhage round the puncture with minute petechial hæmorrhages and congestion in the surrounding area of subcutaneous tissue. The peritoneum and pleura were frequently wet. The lungs were distended and filled the thorax, but there were massive areas of collapse which were fleshy and hæmorrhagic. The surrounding lung was obviously œdematous and was distended with air and fluid. In some animals there were petechial hæmorrhages scattered through the lung substance, but massive hæmorrhages were uncommon. The bronchi and trachea were unobstructed, but contained frothy fluid. The thymus was frequently congested and petechial hæmorrhages were not uncommon. In three or four animals there was excess of bile in the small intestine and in one a congested loop of small bowel had numerous petechiæ in the mucosa and altered blood in the lumen. Hæmoglobinuria was absent in all these animals. In female animals the uterus was invariably congested.

THE EFFECTS IN THE GUINEA-PIG.

The Effect of Intravenous Injection.

Even with large doses injected into the jugular vein under cocaine anæsthesia there were no signs of intravascular coagulation and though death took place with dramatic suddenness, the picture presented was quite different from that produced with other venoms when intravascular thrombosis is the cause of death. In Table VI are set out the results of the injection of large doses of venom administered in a concentration of twenty milligrammes per cubic centimetre.

TABLE VI.

The Effect of Large Doses injected intravenously into Guinea-pigs.

Weight in Grammes.	Dose in Milligrammes.	Death Times.
349	20	Less than 2 minutes.
340	12	Less than 2 minutes.
345	3·45	Less than 2 minutes.
400	2·0	2¾ minutes.

It was extremely difficult to determine the exact moment of death. After the injection the animal quietly subsides into the prone position and respiration ceases in from one minute to one minute and twenty seconds after the injection has been made. The heart continues to beat for some minutes and when its movement can no longer be felt through the thoracic wall, is still found beating if the thoracic cavity is opened within five minutes. The animal which received 3·45 milligrammes, showed a few nodding movements of the head and jerky movements of the body associated with failure of respiration.

At autopsy no trace of clotting was found in the heart or vessels. The blood everywhere was fluid. The clotting time after death in the animal which received the largest dose, was ten minutes and the clot was soft and flabby. In the other three animals the clotting times were five, seven and a half and fourteen minutes and the clot was solid and normal. The musculature of the abdominal wall was intensely congested, as also were the lungs, but there were no other obvious lesions in the organs. The sciatic and median nerves as well as the phrenic nerves were found to be insensitive to faradic stimulation when tested immediately after death while

the heart was still beating, though the muscles contracted readily when stimulated directly.

In Table VII are seen the results obtained in a larger number of animals in which smaller doses were injected intravenously in a concentration of 0·1 milligramme per cubic centimetre.

TABLE VII.

Results of Intravenous Injection in Guinea-pigs.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Death Times.
2	286	0·014	One died in 1 hour 44 minutes and one between 3½ and 5½ hours.
4	316	0·012	Two died between 2 and 4 hours and two between 3 and 5 hours.
4	310	0·010	One died in 1½ hours, two between 2½ and 4½ hours, and one in less than 18 hours.
4	242	0·008	Three died in less than 20 hours and one in 24 hours.
6	261	0 006	Two died in less than 20 hours, three on the second day, and one on the third day.
2	260	0·004	Both survived without definite symptoms.

The certainly lethal dose is therefore 0·006 milliramme per hundred grammes or 0·06 milligramme per kilogram.

Symptoms.

With doses from 0·014 to 0·010 milligramme per hundred grammes there were no symptoms during the first hour after the injection. The onset of symptoms occurred during the next half hour with dyspnœa and occasional obstructive cough. The nose was wet and the coat ruffled. In two animals only was there paresis of the hind limbs. One or two animals at this stage were lying prone in a collapsed condition with occasional jerky attempts to force air into the lungs. There was no obvious cyanosis and no convulsions were observed. With doses near the certainly lethal dose (0·008 and 0·006 milligramme per hundred grammes) there were only slight symptoms in eight hours, though a few had dyspnœa, wet noses and ruffled coats. In twenty hours those which had not succumbed, had severe symptoms. Dyspnœa and outpouring of fluid from the nose and mouth were the outstanding phenomena. In one or two there was also paresis of the hind limbs.

Post Mortem Findings.

The clotting time was normal in two animals, but was not observed in the others, as the autopsy was carried out some time after death, though before the onset of rigor. In these the blood had clotted in the heart, but remained fluid in the vessels. There was no hæmoglobinuria. The lungs were intensely congested, in some hæmorrhagic and in all œdematous. The adrenals and in females the uterus were likewise congested. The spleen was not enlarged, but the small intestine was intensely congested in most of the animals. In some there was blood-stained fluid in the lumen of the bowel. There were no signs of *ante mortem* thrombosis in the mesenteric vessels or elsewhere.

The Effects of Subcutaneous Injection.

The results of subcutaneous injection in the guinea-pig are shown in Table VIII, where are to be found the data for the determination of the "characteristic" for this venom (see Graph I). The animals weighed from 240 to 310 grammes and the venom was injected in a concentration of 0·1 milligramme per cubic centimetre.

TABLE VIII.

Results of Subcutaneous Injection in Guinea-pigs.

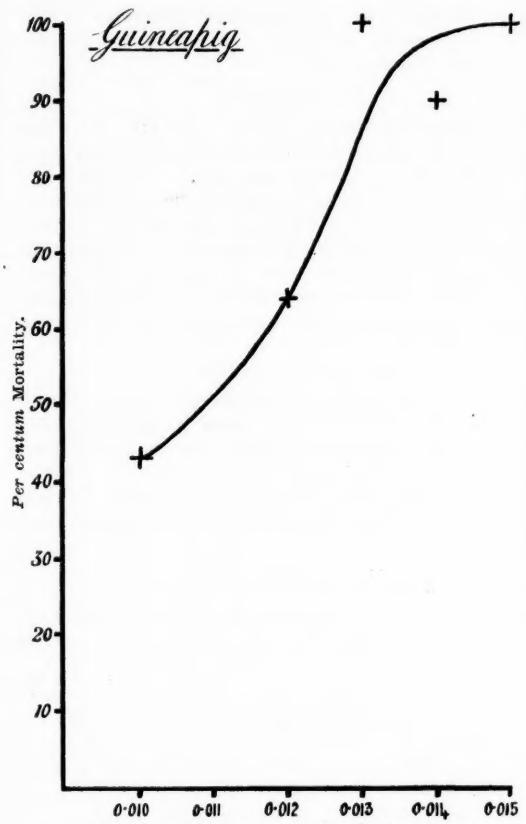
Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Mortality. %	Death Times.
23	285	0·015	100	One died in 3 hours, fourteen in between 3 and 16 hours, four later on the first day, two on the second day, and two on the third day.
10	265	0·014	90	One died in less than 18 hours, one in 20 hours, one in 21 hours, one in 23 hours, four on the second day, one on the third day, and one survived.
24	282	0·013	100	Thirteen died in less than 15 hours, one in 15 hours, one in less than 21 hours, one in 23 hours, six on the second day, one on the third day, and one on the fourth day.
22	267	0·012	64	One died in 6½ hours, one in 9 hours, three in less than 18 hours, six on the second day, two on the third day, one on the fifth day, and eight survived.
14	254	0·010	43	One died in 9½ hours, four died on the second day, one on the third day, and eight survived.

The certainly lethal dose for guinea-pigs weighing from 260 to 285 grammes is 0·015 milligramme per hundred grammes or 0·15 milligramme per kilogram. The subcutaneous-intravenous index is 2·5.

The survival of one guinea-pig of ten injected with 0·014 milligramme per hundred grammes has made the results somewhat irregular and has exercised an undue effect owing to the small number in the group. This animal was the smallest of the group, weighing 260 grammes. The curve has been drawn midway between the second and third points. This irregularity indicates the importance of uniformity of body weight in such estimations of toxicity. It is likely that the certainly lethal dose for guinea-pigs of 280 grammes weight is less than 0·015 milligramme per hundred grammes.

The Symptoms.

The earliest symptoms in animals injected with doses of this order are respiratory. There is dyspnœa with audible respirations. The nose is wet and there is excess of secretion, either salivary or from the respiratory passages. The coats are staring and the animals are quiet, without obvious cyanosis



GRAPH I.

Characteristic of the venom of the death adder administered subcutaneously in guinea-pigs.

or convulsive movements. After eighteen hours, for example, in some of the animals which received 0·012 milligramme per hundred grammes, there was obstructive cough, dyspnœa and in a few slight cyanosis. In the group which received 0·014 milligramme per hundred grammes, nearly all the animals were severely affected at this stage. They sat huddled up with staring coats and wet noses. Dyspnœa with laboured, audible breathing was the most striking symptom; a few had obstructive cough. Most were quiet, but in one or two of the more severely affected there were head nodding movements. The pupils were moderately dilated (one-half to two-thirds their maximal size). No paresis was evident at this stage. After thirty hours there was some weakness of the hind limbs and neck muscles, but respiratory symptoms were still dominant. After forty-four hours the more severely ill of the survivors were collapsed, some flat out in the prone position, and even among these only a few appeared to have definite paralysis. When paralysis was present at this stage, the limb and neck muscles were severely affected. The condition was, however, complicated by cardio-vascular failure. A few had general muscular tremor, weakness of the hind limbs and occasional starting movements. For the most part the excessive secretion from the mouth and nose had dried up at this stage.

Post Mortem Findings.

The most striking feature was the invariable presence of massive hæmorrhages with œdema in the lungs. In some animals there were extensive areas of collapse. The bronchi in many contained frothy fluid. The bowel was empty of fluid and in some animals was distended with gas. The gall bladder was full of bile and in many animals there was excess of bile-stained fluid in the intestine. The pancreas and adrenals and in the female the uterus were congested. Hæmoglobinuria was not observed, though since the bladder was found empty at autopsy, this symptom may have been missed in some animals. Very few showed any obvious lesion at the site of inoculation in the abdominal wall. The clotting time was normal, two and a half to three minutes.

EFFECTS IN THE RAT.

The Effect of Intravenous Injection.

After preliminary ranging experiments a large number of rats was injected with the venom intravenously. It was used in a concentration of 0·1 milligramme per cubic centimetre in saline solution and injected into a tail vein. The results are shown in Table IX.

TABLE IX.

Results of Intravenous Injection in Rats.

Number of Animals.	Weight or Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Mortality. %	Death Times.
1	157	0·06	—	Died in 12 minutes.
1	162	0·04	—	Died in 1 hour 50 minutes.
12	146	0·02	100	Three died in 1½ hours, one in 1¾ hours, one in 2 hours, one in 3 hours 10 minutes, one in 4½ hours, one in 7½ hours, two in less than 20 hours, one in 23 hours, and one in 26 hours.
12	143	0·018	83	One died in 3¼ hours, one in 5 hours, one in 6½ hours, one in 17½ hours, one in 24 hours, one in 30 hours, one in 50 hours, one in 54¼ hours, two on the third day, and two survived.
10	140	0·016	80	One died in 6 hours, one in less than 16 hours, one in 21 hours, one in 24 hours, three on the second day, one on the third day, and two survived.
2	130	0·014	—	Both had moderately severe symptoms, but survived.
2	109	0·012	—	One died on the third day and one survived.
4	148	0·010	—	One had slight symptoms, all survived.
3	137	0·008	—	All survived, without symptoms.

The certainly lethal dose is 0·02 milligramme per hundred grammes or 0·2 milligramme per kilogram for rats of about 145 grammes weight. The numbers

of animals are insufficient to characterize the venom for this species.

The Symptoms.

There were no symptoms immediately following any of the injections. With doses of from 0·016 to 0·02 milligramme per hundred grammes there were obvious respiratory symptoms within two to three hours. The coats were ruffled and there was excessive flow of fluid from the mouth. The breathing was laboured and *râles* might be felt through the chest wall. At this stage there was no paralysis. After six to seven hours respiratory embarrassment was still more evident, but there was no paralysis even of the hind limbs. Among the survivors after twenty-four hours there were a few with paralysis, but this was at no time a striking feature. Many were collapsed and lying prone. Death was quiet without convulsions.

Rats which received smaller doses presented only respiratory symptoms. There was dyspnœa with wet breathing and excess of secretion from the mouth. The coats were often staring and complete recovery ensued in all but one animal within twenty-four to forty-eight hours.

Post Mortem Findings.

The outstanding features were œdema, congestion and hæmorrhages, massive or petechial, in the lungs. A few animals had excess of bile-stained secretion in the small intestine. There was no *ante mortem* clotting, the heart and vessels containing fluid blood at autopsy. The blood taken from the heart immediately after death clotted in from two and three-quarters to three minutes. In none of the animals was hæmoglobinuria found.

The Results of Subcutaneous Injection.

A few rats were injected subcutaneously in the tissues of the left thigh. The venom was used in a concentration of 0·1 milligramme per cubic centimetre. The results are set out in Table X.

TABLE X.

Results of Subcutaneous Injection in Rats.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 100 Grammes.	Results.
4	106	0·05	One died in 4 hours, one in 11 hours, one in 22 hours, and one in 25 hours.
9	128	0·04	One died in 5 hours, one in 6 hours, two in less than 24 hours, two on the second day, and three on the third day.
6	155	0·035	One died in 3½ hours, three in less than 22 hours, one in 36 hours, and one survived.
2	128	0·03	Both had severe symptoms, but survived.
2	130	0·025	One had moderate symptoms, both survived.
2	130	0·02	Both had slight symptoms, but survived.
2	176	0·01	Neither presented any symptoms.

The certainly lethal dose by the subcutaneous route for rats of about 130 to 150 grammes weight is 0·04 milligramme per hundred grammes or 0·4 milligramme per kilogram. The subcutaneous-intravenous index is 2·0.

The Symptoms.

The symptoms were closely similar to those observed following intravenous injection, but were slower in onset. Nearly all had wet noses and ruffled coats and the embarrassed, heavy breathing was the most striking effect of the venom. A few were paralysed in the hind limbs on the second day. Collapse and weakness were evident in all before death. There were no convulsions at any stage and starting movements were observed only in one or two animals.

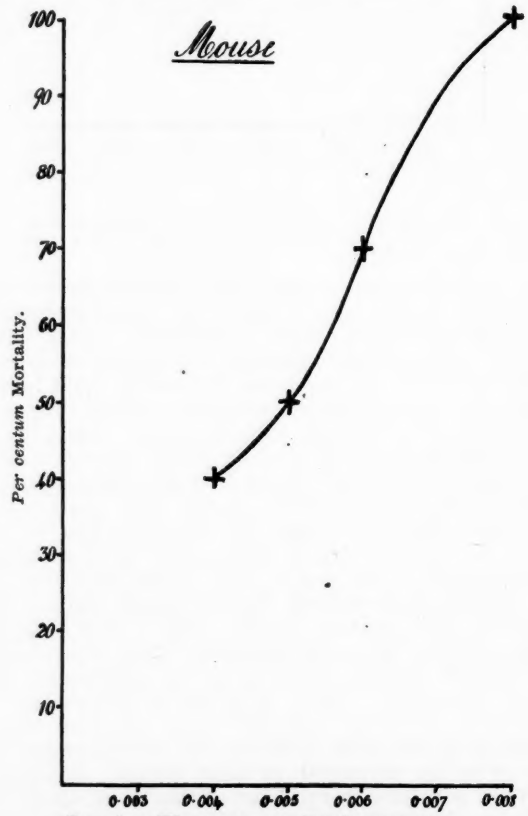
Post Mortem Findings.

There were no pathological changes at the site of injection. In only one animal was the urine faintly blood stained. A few animals had excess of bile-stained fluid in the small bowel. Nearly all had congested lungs with petechial or massive hæmorrhages. There were no other obvious pathological changes.

EFFECTS IN THE MOUSE.

Results of Intravenous Injection.

The absence of intravascular clotting following the intravenous injection of death adder venom



GRAPH II.

Characteristic of the venom of the death adder administered intravenously in mice.

made it possible to determine its characteristic by intravenous injection. The mice used were mixed, some albinos and some coloured. The sexes were fairly evenly distributed and the weight of the animals ranged from fifteen to thirty-two grammes, the great majority weighing between nineteen and twenty-four grammes. The venom in a concentration of 0·02 milligramme per cubic centimetre was injected into one of the caudal veins and the rate of injection was as slow and uniform as possible. The data for the characteristic (see Graph II) are given in Table XI.

TABLE XI.
Results of Intravenous Injection in Mice.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 20 Grammes.	Mortality. %	Death Times.
20	19	0·008	100	One died in 1¼ hours, three in 1 hour 40 minutes, two in 1 hour 50 minutes, five in 2 hours, one in 3 hours, one in 3½ hours, one in 5 hours, one in 5¾ hours, one in 7½ hours, one in 9½ hours, one in 10 hours, and two later on in the first day.
30	22	0·006	70	One died in 26 minutes, one in 50 minutes, two in 1 hour 34 minutes, one in 1¾ hours, two in 2 hours, one in 3 hours, one in 3½ hours, one in 5 hours, one in 6 hours, five later on in the first day, two on the second day, one on the third day, one on the fourth day, one on fifth day, and nine survived.
30	21	0·005	50	Two died in 3¾ hours, one in 6 hours, seven later on in the first day, three on the second day, one on the third day, one on the fourth day, and fifteen survived.
30	22	0·004	40	One died in 4¼ hours, one in 5 hours, one in 8¾ hours, three others during the first day, three on the second day, one on the third day, two on the fourth day, and eighteen survived.
4	22	0·003	—	All survived.

The certainly lethal dose is 0·008 milligramme per twenty grammes or 0·4 milligramme per kilogram.

The Symptoms.

There were no immediate symptoms with this range of dosage. With the smallest doses a few animals were affected in from eight to nine hours. Their coats were ruffled; in some dyspnœa was the striking feature and in others paralysis of the hind limbs. With larger doses these symptoms appeared earlier. Generally speaking dyspnœa was an earlier symptom than paralysis. When paralysis occurred, the hind limbs were first affected and at a later stage collapse was evident, the animals lying prone without starting movements. Death occurred with respiratory failure and without asphyxial convulsions. Hæmoglobinuria was infrequent. There were no symptoms suggestive of intravascular thrombosis.

Post Mortem Findings.

In all cases in which autopsy was carried out shortly after death, the blood was fluid and there was no thrombosis anywhere. The spleen was not enlarged nor were the intestines congested. In nearly all there was either congestion of the lungs or hæmorrhage, petechial or massive. Nearly all had excess of bile-stained fluid in the small intestine. In a few there were petechial hæmorrhages in the thymus. Hæmoglobinuria was found in about 25% (thirteen in forty-nine autopsies). Careful microscopical examination disclosed renal casts formed of blood pigment in one animal, but only a few ghosts or red blood cells were present in any of the specimens examined.

The effect of larger intravenous doses on the death times are seen in Table XII.

TABLE XII.
Effect on Variation of Dosage on the Death Time in Mice.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 20 Grammes.	Death Times.
3	22	0·1	Two died in 4 minutes and one in 20 minutes.
2	27	0·02	Died in 14 and 17 minutes.
2	22	0·01	Died in 1 hour 4 minutes and 1 hour 20 minutes.

The symptoms were similar to those already described, but earlier and more dramatic in onset. There were no immediate symptoms and no signs of intravascular clotting at autopsy.

The Effect of Subcutaneous Injection.

The venom was injected in a concentration of 0·02 milligramme per cubic centimetre into the subcutaneous tissues of the left flank. The results are seen in Table XIII.

TABLE XIII.
Results of Subcutaneous Injection in Mice.

Number of Animals.	Average Weight in Grammes.	Dose in Milligramme per 20 Grammes.	Death Times.
10	19	0·014	Six died in less than 2 hours 40 minutes, three in 3 hours 50 minutes, and one in 4 hours.
10	21	0·012	One died in 2 hours 20 minutes, one in 2 hours 35 minutes, two in 3 hours 40 minutes, one in 4 hours, one in 4½ hours, one in 5 hours 5 minutes, one later on in the first day, one on the fourth day, and one survived.
9	18	0·010	One died in 2 hours 10 minutes, one in 3 hours 5 minutes, one in 7 hours, one in 7½ hours, one later on in the first day, one on the fourth day, and three survived.
10	20	0·008	One died in less than 17 hours, one in 22 hours, one on the second day, two on the fourth day, and five survived.

The certainly lethal dose for mice of about this weight is 0·014 milligramme per twenty grammes or 0·7 milligramme per kilogram. The subcutaneous-intravenous index for this species is 1·75.

The Symptoms.

The symptoms are not significantly different from those exhibited by mice injected intravenously, but are somewhat slower in onset. Dyspnœa is a more frequent and dominant symptom than paralysis. In the animals of the last group, after seventeen hours all were more or less severely affected. The coat was staring and nearly all had dyspnœa. In a few weakness of the hind limbs was also present. Hæmoglobinuria was not very frequent.

Post Mortem Findings.

All showed hæmorrhages and œdema of the lung, in a few there were minute hæmorrhages in the adrenals and all had excess of bile-stained fluid in the small intestine. Of seventeen mice examined there were three with hæmoglobinuria.

SUMMARY OF THE CERTAINLY LETHAL DOSE OF DEATH ADDER VENOM FOR THE SPECIES STUDIED.

In Table XIV I have summarized the certainly lethal dosage of this venom for the species investigated, including Fairley's(1) observations on sheep.

TABLE XIV.

The Certainly Lethal Dosage of Death Adder Venom.

Species.	Intravenous Certainly Lethal Dose in Milligramme per Kilogram.	Subcutaneous Certainly Lethal Dose in Milligramme per Kilogram.	Subcutaneous-intravenous Index.
Horse ..	—	0·04[1]	—
Sheep ..	0·028[1]	0·025	Less than unity
Monkey ..	—	0·15[1]	—
Cat ..	—	0·5[1]	—
Rabbit ..	0·12	0·15	1·25
Guinea-pig	0·06	0·15	2·5
Rat ..	0·2	0·4	2·0
Mouse ..	0·4	0·7	1·75

[1] Only approximate.

The cat, rat and mouse are more resistant to the action of this venom than the monkey, rabbit and guinea-pig. The horse and sheep are more susceptible than this last group. No indication is afforded of the certainly lethal dose for man, save that it probably lies between 0·025 and 0·15 milligramme per kilogram. The symptoms exhibited by animals of the species investigated here and the autopsy findings indicate that the venom has a complex action. Its hæmolytic activity is indicated by the results obtained in the horse. Hæmoglobinuria was not observed in the monkey, cat, rabbit, guinea-pig and rat and was infrequent in the mouse. The most striking features in many of the species were the respiratory symptoms apparently related to the lung lesions, œdema and hæmorrhage, which were intense in the horse, cat, rabbit, guinea-pig, rat and mouse. In the monkey, though similar symptoms were presented, the lungs were neither œdematous nor hæmorrhagic. The bulbar paralysis in the horse and the quiet mode of death, without convulsions, in this and other species, despite termination by respiratory failure, indicate the powerful neurotoxic properties of the venom. It is, however, difficult to differentiate neurotoxic activity in the presence of collapse of cardio-vascular origin.

The results of intravenous injections negative the presence of thrombase in this venom and the clotting time of samples of blood taken from the heart immediately after death suggest that it is only weakly anticoagulant, since large doses are required to produce any considerable delay in clotting time.

The venom, therefore, is powerfully hæmorrhagic and neurotoxic, not coagulant, but on the contrary weakly anticoagulant. It is also hæmolytic in action.

CONCLUSIONS.

1. The venom of the death adder is highly toxic to all the species examined, the subcutaneous certainly lethal dose lying between 0·025 and 0·7 milligramme per kilogram.
2. The subcutaneous-intravenous index varies in the species examined from 2·5 to about unity.
3. The symptoms and *post mortem* findings indicate that like other venoms, that of the death adder is complex in action, possessing neurotoxic, hæmorrhagic and hæmolytic activity. The venom is not coagulant, but on the contrary exhibits a feeble anticoagulant action.

My thanks are due to Dr. N. H. Fairley who collected the venom, to Miss Beryl Splatt who has weighed it out for use in these experiments, and to Mr. E. Southwood who prepared the graphs in this and in my earlier papers.

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THE ACTION OF THE VENOMS OF THE COPPER-HEAD (*DENISONIA SUPERBA*) AND OF THE DEATH ADDER (*ANCANTHOPHIS ANTARCTICUS*) ON THE COAGULATION OF THE BLOOD.[1]

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THE classical researches of C. J. Martin(1) on the venoms of the tiger snake (*Notechis scutatus*) and

[1] This research was carried out under a grant from the Commonwealth Government Department of Health.

the black snake (*Pseudechis porphyriacus*) demonstrated their striking activity even in extremely small concentrations in causing coagulation of the blood both *in vivo* and *in vitro*. Recent observations by N. H. Fairley[2][3] on the effects of the injection of the venoms of the copper-head and death adder in sheep and my own observations[4][5] on rabbits, guinea-pigs, rats and mice have failed to indicate that either of these venoms has any coagulant action *in vivo*. The changes in the coagulation time in sheep following the injection of these venoms (Fairley[2]) suggest rather that their action is anticoagulant. Phisalix[6] attributes to Lamb the statement that the venom of *Ancanthophis antarcticus* is powerfully coagulant *in vivo*. This I have been unable to verify in Lamb's published papers. Excepting the observations noted above the venom of *Denisonia superba* has not been previously investigated. In the present paper it is shown that while both these venoms in high concentration exhibit a feeble coagulant effect *in vitro*, no corresponding action can be demonstrated *in vivo*. *In vitro* they also produce definite but slight anticoagulant effects.

Calmette[7] and Noguchi[8] have both devoted some space to a consideration of the earlier work on the coagulant action of venoms and an excellent *résumé* of the history of these investigations with a full bibliography is given by Marie Phisalix[6] in her work on *"Animaux venimeux et venins."* I propose, therefore, only to review briefly the main facts which have been established in this regard.

The coagulant action of venoms is confined to those of the vipers and of some Australian elapines. The venoms of most of the colubridæ have no such action. Coagulant venoms when injected intravenously in sufficient dose, cause rapid death from intravascular coagulation. In minute dosage, as Martin[9] showed, the blood is rendered incoagulable and the animal is protected from the subsequent injection of a dose sufficient in an untreated animal to cause coagulation. When blood which has been rendered incapable of spontaneous coagulation either by the addition of citrates, oxalates or fluorides or by the injection of peptone or hirudin, is treated *in vitro* with coagulant venoms rapid clotting ensues (Lamb[10]). The investigation of these phenomena by Martin, Lamb, Mellanby, Arthus and by Houssay and his colleagues has led to the following view of the action of venoms.

The studies of Moravitz[11] first showed that coagulation of the blood proceeded in two phases, the first consisting of the formation of fibrin ferment, thrombin or thrombase, which resulted from the interaction of thrombokinase or cytozyme, derived from damaged tissues or platelets, in the presence of calcium salts on the inactive precursor of thrombin, serozyme, prothrombin or thrombogen. The second phase is that of the action of thrombin on fibrinogen causing the irreversible coagulation of the latter.

The action of coagulant venoms is regarded by the majority of workers as being upon the second phase of coagulation, their activity being thought to be due to the presence in them of a thrombase acting directly upon the fibrinogen. Martin[12] showed that the action of tiger snake venom *in vitro* was independent of the concentration of calcium ions and made the further interesting observation that when a minute dose of venom was used to coagulate a large amount of oxalated plasma, the serum which exuded from the clot, could be used to coagulate a further portion of plasma, the serum from this clot a further quantity and so on for three or four successive coagulations, the phenomenon being limited only by unavoidable adsorption of some of the coagulant substance to the fibrin. The active agent behaves like a ferment in its action at temperatures between 6·3° and 40° C. and in its destruction by heat. On the other hand Mellanby[13] has shown that the venom of the tiger snake acts on solutions containing prothrombin like a kinase, their coagulating power increasing with the time during which the action is allowed to proceed. When plasma is coagulated by venom, the serum which exudes from the clot, also increases in activity with the time during which it is left in contact. This Mellanby attributes to the formation of thrombin. He advances the hypothesis that the active principle of venom is a kinase and that the calcium necessary for the activation of prothrombin is present in the solutions of prothrombin and fibrinogen used to test its activity. He also explains the positive and negative phases following the injection of coagulant venoms. The intravenous injection of venom in sufficient dose causes intravascular thrombosis by massive coagulation of fibrinogen, but, if the dose is smaller and the injection is made more slowly, fibrinogen is altered to fibrin which is removed from the circulation. The negative phase blood so obtained owes its stability to the absence of fibrinogen.

Houssay, Sordelli and their colleagues[14] have more recently investigated the coagulant and anticoagulant properties of twenty different venoms. They accept Mellanby's explanation of the action of coagulant venoms *in vivo* in the production of positive and negative phases. In the negative phase fibrin has been removed by deposition on red blood corpuscles and vascular endothelium. In their *in vitro* experiments they adopted the ingenious method of letting venom act on thrombokinase, prothrombin and fibrinogen and, after neutralizing the venom with antivenine, studying the effects which had been produced on the particular reagent under investigation. All the venoms studied destroy thrombokinase. This they attribute to lipolytic activity. This is the secret of the action of anticoagulant venoms. On the other hand, the coagulant venoms produce their effects by the presence of a special active coagulant substance, thrombin. Many venoms also attack prothrombin and this power, though feebler than their action on thrombokinase, runs parallel with their proteolytic activity. Some venoms also have a destructive action on fibrinogen which also appears to be related to proteolysis.

It must, however, be recognized that among the proteroglyphous colubridæ it is the exception rather than the rule for the blood to possess coagulant powers and that on the contrary the venoms of some members of this group are anticoagulant in action. The most striking example of this is found in the venom of the cobra (*Naia tripudians*) which has a constantly anticoagulant action both *in vivo* and *in vitro* (Lamb[10]). The venoms of *Naia haie, Naia nigricollis, Enhydrina bengalensis, Elaps frontalis, Elaps maregravi* and *Philodryas schotti* also possess this activity in varying degree.

Some venoms which have strongly coagulant action have an anticoagulant effect *in vitro* when present in sufficient concentration. This last phenomenon, notably exhibited by some species of Lachesis, appears to be of a different nature from that exhibited by other venoms in moderate concentrations. It is due to the proteolytic action of the venom, destroying prothrombin and altering fibrinogen (Noc[15]). The venoms which possess anticoagulant powers both *in vivo* and *in vitro*, appear to owe this activity to the presence of an antikinase which destroys thrombokinase and prevents the formation of thrombin from prothrombin. This was shown to be the case for cobra venom by Moravitz. Some venoms, notably that of the cobra, cause the formation of antithrombin *in vivo*.

Effect of Intravenous Injections of the Venoms of the Death Adder and Copper-Head in Large Doses.

It is a well recognized fact that certain venoms which when injected intravenously in moderate doses fail to kill by causing intravascular thrombosis, may do so if the dose is very much increased. For example, Lamb[16] showed this to be so with the venom of *Bungarus fasciatus*.

Fairley[3] has shown that in sheep the intravenous injection of 0·2 milligramme per kilogram of death adder venom, equivalent to eight times the certainly lethal dose, and 0·4 milligramme per kilogram of copper-head venom, equivalent to four times the certainly lethal dose, caused no intravascular clotting. For copper-head my own observations in rabbits showed that one milligramme per kilogram, equivalent to three times the certainly lethal dose, in guinea-pigs two milligrammes per kilogram, equivalent to thirteen times the certainly lethal dose, in rats 1·4 milligrammes per kilogram, equivalent to nearly twice the certainly lethal dose, and in mice two milligrammes per kilogram, equivalent to four times the certainly lethal dose, could be injected intravenously without causing thrombosis. For death adder venom I have shown that thrombosis does not follow intravenous injection in the rabbit of 0·4 milligramme per kilogram, equivalent to three times the certainly lethal dose, in the guinea-pig of sixty milligrammes, equivalent to about one thousand times the certainly lethal dose, and in the mouse of five milligrammes per kilogram, equivalent to twelve times the certainly lethal dose.

The rabbit appears to be peculiarly sensitive in its reaction to venoms containing thrombase as is illustrated by the results of the intravenous injection of tiger snake venom. In my experience a dose of 0·002 milligramme per kilogram of this venom invariably causes intravascular thrombosis in this animal.

The intravenous injection into rabbits of large doses of the venoms of the copper-head and death adder in a concentration of twenty milligrammes per cubic centimetre gave the following results.

Rabbit 1, weighing 1·74 kilograms, received fifty milligrammes of death adder venom injected intravenously into the marginal vein of the ear. Quiet failure of respiration took place within two minutes. There were no convulsions. The pupils were first contracted and at the end of two minutes became somewhat dilated. The heart continued beating after the respirations had failed. The blood was everywhere fluid and there were no clots in the heart, lungs, portal veins or other great vessels. Blood taken from the heart clotted firmly in between thirty-five minutes and one hour. Apart from intense congestion of the lungs there were no obvious *post mortem* changes.

Rabbit 2, weighing 3·42 kilograms, received forty milligrammes of death adder venom injected intravenously. At the end of one minute there were head nodding movements and a few slight backward and forward jerks of the body; the pupils were contracted and respiration ceased finally after two minutes. There were no convulsions. The blood was fluid in the heart and great vessels and there were no clots. The clotting time of a sample of blood taken from the heart immediately after death was twenty-four minutes. The only obvious *post mortem* change was intense congestion of the lungs and of the parietal peritoneum.

Rabbit 3, weighing 2·43 kilograms, received fifty milligrammes of death adder venom injected intravenously. Respiration failed in one minute; the corneal reflex could not be elicited after one minute twenty seconds. The heart was beating vigorously when the thorax was opened. There was no coagulation in the heart or great vessels and the clotting time of blood withdrawn from the heart was forty-one minutes.

Rabbit 4, weighing 3·77 kilograms, received fifty milligrammes of copper-head venom injected intravenously. Death took place in two and a half minutes. Within one minute the head had fallen forward, the corneal reflex could not be elicited and there were exophthalmos and dilatation of the pupils. Convulsive movements rapidly followed, attended by a few ineffectual respirations. The pupils were contracted terminally. The heart was still beating after death, the blood was everywhere fluid, no clots being found. Blood taken from the heart immediately after death clotted in twenty-one minutes.

Rabbit 5, weighing 2·44 kilograms, received forty milligrammes of copper-head venom injected intravenously. The head fell forward at the end of the first minute. The animal then ran round with an ataxic gait and within two minutes failure of respiration ensued. There were exophthalmos, dilatation of the pupils and convulsions. There were a few ineffectual and irregular respirations before death which took place in three minutes. The blood was everywhere fluid and the clotting time of blood withdrawn from the heart was nine minutes.

Rabbit 6, weighing 2·67 kilograms, received forty milligrammes of copper-head venom injected intravenously. There was first a slight increase in the respiration rate and after two minutes the animal was sitting hunched up with the head lying on one side on the floor, the neck muscles having completely lost their tone. During the third minute the respirations became slow and irregular and failed three minutes fifteen seconds after the injection. There were no convulsions, but a few jerky movements of the hind limbs. All movement ceased six minutes after the injection. At autopsy the heart was still beating feebly; the blood was everywhere fluid. The clotting time of blood taken from the heart was eighteen minutes.

Rabbit 7, weighing 2·85 kilograms, received five milligrammes of copper-head venom injected intravenously. There was slight restlessness during the first half hour.

After fifty minutes the head was down and could be raised only with difficulty. After fifty-four minutes the neck muscles had lost their tone. The pupils were contracted and there was dyspnœa. Respiration failed and all movement ceased after sixty-seven minutes. At autopsy the heart was still beating feebly; the lungs and intestines were congested. The blood was everywhere fluid. The clotting time of a sample of blood taken from the heart was twenty-four minutes.

The injection of these large doses of venom intravenously incidentally revealed another interesting phenomenon. After the injection of death adder venom, when the animal was killed immediately after the respiration had failed, the heart was found to be beating vigorously and strong faradic stimuli applied to the sciatic, median and phrenic nerves failed to cause any contraction in the muscles innervated by them, the muscles themselves still being sensitive to weaker stimuli. Two milligrammes of death adder venom injected intravenously into a guinea-pig of four hundred grammes produced similar effects.

With copper-head venom, even with large doses the result was not so striking. The phrenics were not always completely insensitive to faradic stimuli and stimulation of the sciatic nerves caused contraction of the innervated muscles.

Comparison of the clotting times of blood taken from the heart immediately after death suggests that both venoms in this dosage have a slightly anticoagulant action, the clotting time being increased rather more after the injection of death adder than of copper-head venom.

Birds are also very susceptible to the action of coagulant venoms when these are injected intravenously. The effect of tiger snake venom is well illustrated by the following experiments.

Fowl 1, weighing 1·52 kilograms, received 0·1 milligramme of tiger snake venom injected into a wing vein. The bird fell over after thirty seconds and there was one very violent convulsion terminating in death in forty-five seconds. There was almost universal solid clotting in the heart and vessels. A sample of blood obtained from the left side of the heart failed to clot in six hours.

Fowl 2, weighing 2·37 kilograms, received 0·01 milligramme of tiger snake venom injected into a wing vein. The bird staggered within thirty seconds and fell down in forty-five seconds. It convulsed vigorously from one minute to one and a half minutes after the injection, when all movements ceased. There was general intravascular coagulation.

Fowl 3, weighing 2·22 kilograms, received 0·001 milligramme of tiger snake venom injected intravenously. This dose produced no immediate symptoms; the bird survived.

Even large doses of the venoms of the copper-head and death adder when injected intravenously, failed to cause any intravascular clotting, as the following experiments show.

Fowl 4, weighing 2·3 kilograms, received five milligrammes of pooled death adder venom injected intravenously. Within one minute the bird developed an ataxic gait and sat down. By the end of the second minute the head had fallen forward and the bird remained quiet in this position with regular respirations and no sign of cyanosis till the end of the fifth minute. From this time, when the respirations appeared to fail, till death seven and a half minutes after the injection there was occasional flapping of the wings and the comb was slightly cyanosed. The heart was not found beating after death, the blood was fluid in all the vessels and no clots were anywhere to be found. Blood taken from the heart did not clot in twenty-four hours.

Fowl 5, weighing 1·54 kilograms, received forty-five milligrammes of primary death adder venom injected intravenously. Quiet death occurred within two minutes. There were no convulsions. The blood was fluid in all the vessels and blood withdrawn from the heart clotted in five and a half hours. No trace of *ante mortem* clot was anywhere to be found.

Fowl 6, weighing 0·92 kilogram, received five milligrammes of pooled copper-head venom injected intravenously. Within the first minute the bird was obviously weak and trembling with a quiet onset of paralysis. By the end of the second minute it was sitting down and its head had fallen forward. There was slight respiratory embarrassment at this stage. For some minutes the fowl was lying down, occasionally raising the head. The respirations became very weak and slow at the end of six minutes. After eight minutes the paralysis was still incomplete and there were occasional movements rather like starting movements. The limbs and wings were flaccid. After twelve minutes the respirations became very feeble and for the first time the comb became slightly cyanosed. There were two or three attempts to leap up with fluttering of the wings, the bird succeeding in raising itself only very slightly from the ground. At death twenty minutes after the injection the comb was obviously cyanosed, but the pupils were not dilated. There were no convulsions. Apart from one or two tiny hæmorrhages in the endocardium there were no lesions at autopsy. The blood was fluid in all the vessels and no clots were found. Blood taken from the heart, which had ceased to beat when the thorax was opened, clotted in between six and twenty hours.

Fowl 7, weighing 1·89 kilograms, received forty milligrammes of primary copper-head venom injected intravenously. The bird fell over in forty seconds and then lay quietly with the head down. Respiration appeared to fail after three minutes and at the end of six minutes the comb was deeply cyanosed. There were slight convulsions, evidently modified by paralysis of the skeletal muscles. The blood was fluid in all the vessels and no *ante mortem* thrombi were found. The portal areas were congested and the blood from the heart had not clotted in twenty-four hours.

These experiments show clearly that the venoms of the copper-head and death adder, even in very large doses, exert no coagulative action *in vivo* in the species tested.

The Action of the Venoms in Vitro.

I next proceeded to investigate the action of the venoms *in vitro* and utilized for this purpose citrated and oxalated plasmas as used first by Lamb,[10] and the plasma of the fowl obtained by bleeding out with extreme care without the addition of any anticoagulant (Delezenne[17]). A number of experiments were made which gave concordant results and as controls the action of the venoms of the cobra, daboia and of the tiger and black snakes were studied at the same time.

In these experiments special attention was paid to the cleanliness of the glassware used. The tubes in which the tests were carried out, were 7·5 centimetres long and 12 millimetres in internal diameter. After preliminary mechanical cleaning with soap and water they were boiled in *aqua regia*, washed out repeatedly with distilled water and finally dried in a hot air oven. Cannulas, pipettes, centrifuge tubes and measuring cylinders were cleaned in concentrated sulphuric acid saturated with potassium bichromate, carefully washed with water and dried. Glassware used for the collection of fowl blood

was coated with paraffin with a melting point of 58° C..

Citrated and oxalated plasmas were prepared by bleeding out fully anæsthetized rabbits and cats through cannulas tied into the carotid artery. The blood flowed into cylinders containing measured amounts of a 1% solution of potassium oxalate or 20% sodium citrate in sterile physiological saline solution. The cannula before insertion was moistened with 2% citrate in saline solution or 1% oxalate solution. Sheep plasma was obtained by mixing freshly drawn blood with an equal volume of 2% sodium citrate in physiological saline solution. The citrated or oxalated blood was centrifuged for ten to fifteen minutes at 3,500 revolutions per minute and the plasma pipetted off with sterile Pasteur pipettes into sterile flasks. Fowl plasma was prepared by bleeding out from the sciatic artery under full ether anæsthesia. A paraffin-coated glass cannula was introduced into the lumen of the vessel isolated between a distal ligature and a proximally placed bulldog clamp. The interior of the isolated part of the vessel was washed out with 2% citrate in physiological saline solution before the cannula was inserted and tied in. On removing the bulldog clip the first ten cubic centimetres of blood which flowed, was discarded and as soon as the blood ceased to flow briskly, its collection in a paraffin-coated centrifuge tube was discontinued. The blood was spun in a large centrifuge for twenty to thirty minutes at 3,500 revolutions per minute. The plasma was then pipetted off with paraffin-coated Pasteur pipettes into a paraffin-coated flask. Plasma collected under these conditions remained fluid at room temperature for ten days.

Experiments with Fowl Plasma.

Fowl plasma is an exceedingly delicate reagent for the detection of the coagulant powers of venoms *in vitro*. The plasma used in Experiment I was unusually susceptible to the action of coagulant venoms.

Experiment I.—Primary venoms, that is the product of the first milking of the snakes, were used in the case of all the Australian venoms. The venoms were put up in dilutions containing in 0·1 cubic centimetre of sterile saline solution ten milligrammes, one milligramme, 0·1 milligramme, 0·01 milligramme and so to 0·0000000001 milligramme. In the case of black, tiger snake and daboia venoms a few further tenfold dilutions were tested. The venom was placed in the bottom of the tubes and the plasma was added from a dropping pipette in a volume of 0·2 cubic centimetre to each tube. The tubes were observed at room temperature 20° to 22° C. for forty-eight hours and during the earlier part of this period were examined at frequent intervals by gently tilting the racks. The rapidly clotting tubes were observed separately and timed with a stop watch.

With cobra venom the tubes containing ten milligrammes of venom became turbid in fifty minutes and those containing one milligramme and one-tenth of a milligramme in less than seven hours. No clotting occurred in any of the tubes.

With death adder venom ten milligrammes gave a weak clot in eight minutes, one milligramme a firm clot in ten minutes and 0·1 milligramme a soft clot in three hours forty minutes. The remaining tubes showed no trace of clotting.

With copper-head venom the tube containing ten milligrammes clotted weakly in twenty-five minutes and those containing one milligramme and 0·1 milligramme became turbid in twenty and forty minutes respectively and clotted feebly in less than ten hours. A dose of 0·01 milligramme caused turbidity in one hour fifty-five minutes and firm clotting in three hours forty minutes. A dose of 0·001 milligramme caused firm clotting in three hours forty minutes, doses of 0·0001, 0·00001 and 0·000001 milligramme gave clotting in less than ten hours. A dose of 0·0000001 milligramme caused firm clotting in twenty hours. Doses of 0·00000001, 0·000000001 and 0·0000000001 milligramme caused no clotting.

In contrast to these results are the control observations made with the venoms of the tiger snake, black snake and daboia.

With tiger snake venom the clotting times of duplicate tubes containing 1·0, 0·1, 0·01 and 0·001 milligramme were 45 and 50, 50 and 50, 50 and 50, 50 and 55 seconds. That of the tube containing 0·0001 milligramme was one minute twenty seconds. A dose of 0·00001 milligramme caused firm clotting in two minutes, of 0·000001 milligramme in two minutes forty seconds, of 0·0000001 milligramme in eleven minutes, of 0·00000001, 0·000000001, 0·0000000001 and 0·00000000001 milligramme in from three to five hours. The remaining tubes to 0·000000000000001 milligramme were firmly clotted in eight hours.

With black snake venom the results given in Table I were obtained.

TABLE I.
Black Snake Venom and Clotting Time.

Dose of Venom in Milligrammes.	Clotting Time.
	Minutes. Seconds.
1·0	0 40
1×10^{-1}	0 45
1×10^{-2}	0 50
1×10^{-3}	1 30
1×10^{-4}	3 55
1×10^{-5}	3 50
1×10^{-6}	4 30
1×10^{-7}	16 0
1×10^{-8}	17 0
1×10^{-9}	19 50
1×10^{-10} to 1×10^{-13}	Less than 1 hour.

In duplicate experiments clotting in ten hours was observed with 0·00000000000000000001 milligramme of this venom.

Of daboia venom ten milligrammes caused turbidity in one and a half hours, but no clotting in forty-eight hours. The clotting times are given in Table II.

TABLE II.
Daboia Venom and Clotting Time.

Dose of Venom in Milligrammes.	Clotting Time.
	Minutes. Seconds.
1·0	6 0
1×10^{-1}	2 30
1×10^{-2}	1 15
1×10^{-3}	1 30
1×10^{-4}	2 0
1×10^{-5}	3 30
1×10^{-6}	11 0
1×10^{-7}	19 0
1×10^{-8}	Less than 37 minutes.
1×10^{-9} to 1×10^{-15}	From 1½ to 8 hours.

Cobra venom gave not a trace of coagulation and furnished an adequate control in addition to several tubes containing 0·2 cubic centimetre of plasma diluted with 0·1 cubic centimetre of saline solution, none of which showed any coagulation. Daboia venom displayed the anticoagulant effect of excess of venom due to the destruction of thrombogen. The most effective concentration for coagulation with this sample of venom on fowl plasma lay

between 0·1 and 0·001 milligramme for 0·2 cubic centimetre of the plasma. Amounts above and below these limits showed delay in the time of coagulation. The venoms of the black and tiger snakes and of daboia all caused coagulation in extremely low concentrations and in comparison with these the coagulant power of the venom of the death adder was trivial, requiring more than 0·5 milligramme per cubic centimetre of plasma for firm clotting. The venom of the copper-head was definitely more active, but the limit of concentration at which clotting was observed was 0·0000005 milligramme for one cubic centimetre of plasma.

Not all samples of fowl plasma display this delicacy as a reagent for coagulant venoms. While other experiments with the plasma used in Experiment I gave concordant results, those performed with another sample showed it to be much less sensitive. Tiger snake venom in a dose of 0·00000001 milligramme clotted 0·2 cubic centimetre of this plasma in less than forty minutes at 20° C., but no smaller dose gave any clotting in forty-eight hours. Death adder venom, like that of the cobra, failed to cause any clotting in forty-eight hours even in a dose of one milligramme. Copper-head venom in this dose caused clotting in two hours twenty minutes, but no clotting was observed with smaller doses during forty-eight hours.

Experiments with Mammalian Plasma.

Experiments with citrated (1%) and oxalated (0·2%) plasma of various species (sheep, rabbit and cat) confirm the results obtained with fowl plasma in indicating that the venoms of the copper-head and death adder, though they exert no coagulant action *in vivo* yet possess feeble coagulant powers *in vitro*. This type of experiment is particularly useful because it is possible by the subsequent addition of that amount of calcium chloride necessary to cause coagulation to ascertain whether a venom possesses any anticoagulant powers (Lamb[10]). The results obtained with all the mammalian plasma were in close agreement and only a few typical experiments are recorded.

Experiment II.—The venoms were tested in doses of one milligramme, 0·1, 0·01 to 0·00000001 milligramme in 0·1 cubic centimetre to which 0·2 cubic centimetre of 0·2% oxalated rabbit plasma was added. The tubes were observed at 37° C.. With copper-head venom the tube containing one milligramme gave a soft clot in two hours and with death adder venom those containing one milligramme and 0·1 milligramme clotted in five and twenty minutes respectively. No clotting occurred in tubes containing smaller doses of either of these venoms. Cobra venom caused no clotting in any dilution tested.

The clotting times for black snake venom in doses of one milligramme and 0·1 to 0·001 milligramme were sixty-five seconds, sixty-five seconds, four minutes and eighteen minutes and the remaining tubes were not clotted in seventeen hours. The clotting times for tiger snake venom in doses of 1·0, 0·1 . . . 0·0000001 milligramme were two minutes, one minute, one minute fifty-five seconds, two minutes fifteen seconds, four minutes, eight minutes, thirteen minutes and fifteen minutes. A dose of 0·00000001 milligramme caused partial clotting in thirty minutes and of 0·000000001 and 0·0000000001 milligramme soft and partial clotting in thirty-six minutes.

The effect of the addition of 0·15 cubic centimetre of 0·5% calcium chloride solution to a duplicate set of tubes after two hours' incubation at 37° C. are set out in Table III. Control tubes containing 0·2 cubic centimetre of plasma and 0·1 cubic centimetre of saline solution with added calcium chloride clotted in five minutes at 25° C..

TABLE III.
Anticoagulant Power of Venoms.

Dose of Venom in Milligrammes.	Clotting Times at 25° C.		
	With Cobra Venom.	With Copper-head Venom.	With Death Adder Venom.
1·0	Not clotted in 20 hours.	Already clotted.	Already clotted.
1×10^{-1}		Soft clot in 27 minutes.	Already clotted.
1×10^{-2}		Soft clot in 21 minutes.	13½ minutes.
1×10^{-3}		21 minutes.	13 minutes.
1×10^{-4}		Firm clot in 12 minutes.	15 minutes.
1×10^{-5}	14 minutes.		13 minutes.
1×10^{-6}	13 minutes.		13 minutes.
1×10^{-7}	12 minutes.		11 minutes.
1×10^{-8}	11 minutes.		10 minutes.

It appears from this experiment with mammalian plasma that the coagulant action of these two venoms *in vitro* is much more feeble than was suggested by Experiment I with fowl plasma. The less sensitive nature of the reagent is indicated by the results with black snake venom which instead of being active in a dose of 1×10^{-19} milligramme failed to exert any action in a dose of 0·0001 milligramme. Copper-head venom in a dose of one milligramme gave incomplete coagulation in two hours and that of the death adder failed to clot in doses smaller than 0·1 milligramme. A comparison of the anticoagulant action of the venoms of the death adder and copper-head with the well known powerful action of cobra venom shows that both venoms are only feebly anticoagulant, death adder being less potent than copper-head.

The much less evident coagulant action of venoms on mammalian plasma is well illustrated by the following experiment with rabbit citrated plasma (1%) in which I failed to demonstrate any coagulant action with either of these venoms *in vitro*.

Experiment III.—The following results were obtained in tubes in which no calcium chloride was added with venoms in dosage of five milligrammes, two milligrammes, 0·2 milligramme, 0·02 milligramme, 0·002 milligramme, 0·0002 milligramme, 0·00002 milligramme, 0·000002 milligramme, 0·0000002 milligramme, 0·00000002 milligramme, 0·000000002 milligramme and 0·0000000002 milligramme in 0·1 cubic centimetre of saline solution added to 0·2 cubic centimetre of 1% citrated rabbit plasma. The tubes were incubated for four hours at 37° C. and afterwards observed at room temperature (20° to 22° C.) for forty-four hours.

With copper-head venom no clotting occurred in any of the tubes. There was early turbidity of the three tubes containing the largest dosage of venom and in these a precipitate appeared during incubation.

With death adder venom neither turbidity nor clotting occurred in any of the tubes within forty-eight hours.

With cobra venom turbidity appeared in all the tubes of varying degree but no clotting in forty-eight hours.

With daboia venom in dosage of ten milligrammes no coagulation appeared in ten hours, of two milligrammes a soft clot appeared between one and ten hours, of 0·2 milligramme firm clotting occurred between one and ten hours, of 0·02 milligramme firm clot in between one and ten hours. No clotting in the other tubes after ten hours.

With tiger snake venom the dosage used was one milligramme, 0·1, 0·01 to 0·000000000000001 milligramme. The tubes were not incubated and were observed at 19° to 20° C.. The clotting times in successive tubes to 0·0000001 milligramme as follows: Two minutes, one minute forty-five seconds, one minute fifty seconds, three minutes ten

seconds, nine minutes (soft clot), three and a half hours, between six and fifteen hours and four and a half hours. Smaller doses than 0·0000001 milligramme failed to cause clotting in fifteen hours.

With black snake venom the dosage of one milligramme, 0·1 to 0·000000000000001 milligramme was used; the tubes were not incubated; they were observed at 19° to 20° C.. The first five tubes clotted in the following times: Two and a quarter minutes, two and a quarter minutes, two minutes, eight minutes, one hour ten minutes (soft clot). Doses smaller than 0·0001 milligramme produced no clotting in twelve hours.

A 0·5% calcium chloride solution in a dose of 0·3 cubic centimetre caused normal controls (0·2 cubic centimetre of plasma with 0·1 cubic centimetre of saline solution) to clot in ten minutes at 37° C.. This amount of calcium chloride was added to a series of tubes containing various doses of copper-head, death adder and cobra venom together with 0·2 cubic centimetre of plasma, after they had been incubated for two hours at 37° C.. Table IV shows the clotting times observed during twelve hours at room temperature (20° to 22° C.).

TABLE IV.

Clotting Times at 20°–22° C. after the addition of Calcium Chloride.

Dose of Venom in Milligrammes.	Clotting Time.		
	With Cobra Venom.	With Copper-head Venom.	With Death Adder Venom.
5	No clot in 12 hours.	No clot in 12 hours.	Soft clot in 12 hours.
2		No clot in 12 hours.	Soft clot in 1 hour 25 minutes.
2×10^{-1}			Clotted in 12 hours.
2×10^{-2}			Clotted in 12 hours.
2×10^{-3}	Weak in 55 minutes.	Clotted firmly in 12 hours.	Partial 1 hour 40 minutes
2×10^{-4}			Soft 85 minutes.
2×10^{-5}	46 minutes.		28 minutes.
2×10^{-6}	46 minutes.		28 minutes.
2×10^{-7}	46 minutes.		28 minutes.
2×10^{-8}	46 minutes.		28 minutes.
2×10^{-9}	46 minutes.	38 minutes.	28 minutes.
2×10^{-10}	46 minutes.	44 minutes.	24 minutes.

The results obtained in this and other experiments with rabbit plasmas are in agreement in indicating that the anticoagulant action of the death adder and copper-head venom is slight and that that of the former is significantly feebler in this respect. In this particular experiment copper-head venom exhibits this activity over a longer range than usual. It seemed likely that this anticoagulant action might be due to a proteolytic ferment altering the fibrinogen and so preventing coagulation. After forty-eight hours I therefore tested the uncoagulated tubes of the series to which calcium chloride had not been added, with a dose of black snake venom (0·0005 milligramme) sufficient to clot control tubes in from two to two and a half minutes at 22° C.. The results are instructive and are presented in Table V.

According to Noc[15] and Calmette[7] cobra venom can to some extent inhibit the coagulant effect of Lachesis venom *in vitro*. Lamb showed that even a large dose of cobra venom did not prevent daboia venom from coagulating citrated plasma. Mellanby[13] proved that cobra venom did not prevent the coagulation of plasma by tiger snake venom. Houssay, Sordelli and Negrete confirmed Lamb and Mellanby's observations with the use of mixtures of cobra venom and that of Lachesis. They observed, however, that if the anticoagulant venom were present in sufficient dosage to exert proteolytic action and if the coagulant venom were present in such dosage as to produce coagulation only after the lapse of some minutes, coagulation might be delayed.

TABLE V.

Results of Addition of Black Snake Venom to Tubes containing Mixtures of Venom and Plasma and Remaining Uncoagulated After Twenty-four Hours.

Dose of Venom in Milligrammes.	Clotting Time.		
	With Cobra Venom.	With Copper-head Venom.	With Death Adder Venom.
5	Not coagulated in 24 hours.	Soft partial clot in 17 minutes.	Partial soft clot in 22 minutes.
2			
2×10^{-1}	Soft 17 minutes.		11 minutes.
2×10^{-2}	20 minutes.		9 minutes.
2×10^{-3}	14 minutes.	2¼ minutes.	4 minutes.
2×10^{-4}	14 minutes.	2½ minutes.	3 minutes.
2×10^{-5}	6½ minutes.	2½ minutes.	3 minutes.
2×10^{-6}	3 minutes.	4 minutes.	3 minutes
2×10^{-7}	7 minutes.	4 minutes.	2½ minutes.
2×10^{-8}	2 minutes.	5 minutes.	2½ minutes.
2×10^{-9}	2 minutes.	2 minutes.	2½ minutes.
2×10^{-10}	2 minutes.	2 minutes.	2½ minutes.

In the experiment described here we are concerned, however, not with the action of a mixture of venoms on plasma, but with the coagulant effect of a venom acting on a plasma which had been subjected for twenty-four hours to the action of varying doses of feebly anticoagulant venoms. It should be noted, however, that the possibility of bacterial action was not excluded.

Doses of copper-head and death adder venom equivalent to twenty-five and ten milligrammes per cubic centimetre of plasma, though they interfered with clotting, did not prevent it, while similar amounts of cobra venom made the plasma incoagulable. The venom of the death adder was effective in delaying coagulation to 0·002 milligramme, that of the copper-head to 0·02 milligramme and that of the cobra to 0·0002 milligramme.

A number of other experiments with rabbit plasma gave results similar to those already recorded. In one experiment the venoms of the copper-head and death adder showed no coagulant action after one and a half hours at 37° C. and forty-four hours at 22° C. when tested upon 0·5 cubic centimetre of citrated plasma in doses of 4·0, 2·0, 1·0, 0·5, 0·25, 0·125, 0·06, 0·03, 0·015 and 0·0075 milligrammes.

In an experiment with another sample of citrated rabbit plasma with the use of the same range of dosage of venoms, but only 0·1 cubic centimetre of plasma, the equivalent dose of venom being therefore five times as great as in the case just mentioned, there was no clotting with death adder venom, but the serum in the tubes containing four and two milligrammes of copper-head venom clotted firmly in two hours and that in those containing one milligramme and 0·5 milligramme the clotting was weak in two and two and a half hours at 37° C..

Experiments with Sheep Plasma.

In the experiments with sheep plasma the plasma was diluted with an equal volume of saline solution and they were therefore complicated to some extent

by this dilution effect which has been shown by Houssay[18] to operate in lengthening the coagulation time. In all the experiments full series of controls were used and cobra, tiger snake and black snake venoms were studied over the same range of dosage as the venoms of the copper-head and death adder.

Only one experiment is recorded in which parallel observations were made with sheep citrated plasma and rabbit oxalate plasma. The venoms behaved in the same way with both forms of plasma, though owing to dilution coagulation in the sheep plasma was somewhat slower.

Experiment IV.—A 1·0% citrated sheep plasma was used in amounts of 0·2 cubic centimetre; the doses of venoms were added in 0·1 cubic centimetre of saline solution and the experiment was conducted at a temperature of 23° C..

The first series was carried out without the addition of calcium salts.

TABLE VI.

Clotting Times with Tiger and Black Snake Venoms.

Dose of Venom in Milligrammes.	Clotting Time.	
	With Tiger Snake Venom.	With Black Snake Venom.
1·0	3 minutes.	Turbid, weak clot in 17 minutes.
1×10^{-1}	2 minutes 45 seconds.	2 minutes 30 seconds.
1×10^{-2}	3 minutes 45 seconds.	3 minutes 45 seconds.
1×10^{-3}	8 minutes.	6 minutes.
1×10^{-4}	15 minutes.	35 minutes.
1×10^{-5}	29 minutes.	Not clotted in 24 hours.
1×10^{-6}	32 minutes.	Not clotted in 24 hours.
1×10^{-7}	Soft clot in 2½ hours.	Not clotted in 24 hours
1×10^{-8}		
1×10^{-9}		
1×10^{-10}		

With copper-head venom the serum in the tubes containing one milligramme became turbid and a soft clot formed in one hour. With death adder venom the serum in the tubes containing one milligramme was clotted in five minutes and that in those containing 0·1 milligramme was clotted in thirty-five minutes. The serum in none of the tubes containing cobra venom clotted in twenty-four hours.

The second series of results was read after the addition of calcium chloride.

After incubation for two hours at 37° C. the addition of 0·3 cubic centimetre of 0·5% calcium chloride solution in physiological saline solution caused the controls to clot in six minutes.

The clotting times of the serum in tubes containing death adder, copper-head and cobra venoms after the addition of calcium chloride are shown in Table VII.

TABLE VII.

Clotting Times of Sheep Citrated Plasma treated with Cobra, Copper-head and Death Adder Venoms after addition of Calcium Chloride.

Dose of Venom in Milligrammes.	Clotting Time.		
	Cobra.	Copper-head.	Death Adder.
1×10^{-1}	Not clotted in 13 hours.	Weak 1 hour.	Already clotted.
1×10^{-2}	17 minutes.	35 minutes.	Soft 11 minutes
1×10^{-3}			
1×10^{-4}	14 minutes.	Soft 15 minutes.	10½ minutes.
1×10^{-5}	9 minutes.	10½ minutes.	10 minutes.
1×10^{-6}		8 minutes.	9 minutes.
1×10^{-7}		8 minutes.	8½ minutes.
1×10^{-8}		8 minutes.	

Anticoagulant Effects of Venoms.

Another set of tubes had placed in them 0·1 cubic centimetre of saline solution containing 0·001 milligramme of tiger snake venom. This caused the serum in the control tubes to clot in three and a half minutes.

The result in tubes containing cobra and copper-head venoms in doses of 1·0, 0·1, 0·01 to 0·00000001 milligramme after twenty-four hours at 25° C. and of a similar series with rabbit oxalate plasma and cobra, copper-head and death adder venoms are set out in Table VIII. For the rabbit oxalate plasma the clotting time of the controls was two minutes.

It will be seen that death adder venom has very little action on the rabbit oxalate plasma, causing only trivial delay in the coagulation time with tiger snake venom, whereas the venoms of the copper-head and cobra in doses of 1·0, 0·1 and 0·01 milligramme have a definite delaying or inhibiting action. This effect requires further investigation under conditions in which the possibility of bacterial action is excluded.

The Effect of Heat on the Active Constituents of Copper-Head and Death Adder Venoms.

A number of experiments was made with the use of citrated sheep and oxalated rabbit and cat plasma to determine the effect of heat on solutions of the venom. In the experiment reported here which is typical, the venom solutions were made up in a concentration of five milligrammes per cubic

TABLE VIII.

Dose of Venom in Milligrammes.	Clotting Time.				
	With Cobra Venom and		With Copper-head Venom and		With Death Adder Venom and Rabbit Serum.
	Sheep Serum.	Rabbit Serum.	Sheep Serum.	Rabbit Serum.	
1	Soft 18 hours.	Not clotted in 10 hours.	Not clotted.	Partial soft in 13 minutes.	Already clotted
1×10^{-1}	1 hour.			Soft in 10 minutes.	Already clotted.
1×10^{-2}	8 minutes.	22 minutes		10 minutes.	3½ minutes.
1×10^{-3}	Soft and partial in 7 minutes.	11 minutes.	All soft clot in 7 to 8 minutes; firm in 9 minutes.	4 minutes	3½ minutes.
1×10^{-4}		9 minutes.		2 minutes 50 seconds	2 minutes 45 second..
1×10^{-5}		4½ minutes.			
1×10^{-6}		3 minutes.			2 minutes.
1×10^{-7}		2 minutes.		2½ minutes.	2 minutes.
1×10^{-8}		2 minutes.		2 minutes.	2 minutes.
Control	3½ minutes.	2 minutes.	3½ minutes.		

centimetre in saline solution. These were divided into four parts: one portion was unheated, one heated in a water bath for thirty minutes at 60° C., another thirty minutes at 80° C. and the last for fifteen minutes at 100° C.. The solutions were carefully made up to their original volume with distilled water and eight successive fourfold dilutions were made. A volume of 0·2 cubic centimetre of each of these was then put up with 0·2 cubic centimetre of each kind of plasma. The tubes were incubated two hours at 37° C. and then 0·3 cubic centimetre of 0·5% calcium chloride solution was added to the tubes containing citrated sheep plasma and half this amount to the tubes containing rabbit oxalate plasma. The tubes were then observed at 37° C.. The results with sheep citrated plasma are shown in Table IX. Those with rabbit oxalate plasma were similar save that the serum of the control and of the experimental tubes clotted in shorter time, doubtless owing to the much smaller dilution effect.

This experiment and others which yielded similar results, show that the anticoagulant effect induced by incubation for two hours with copper-head and death adder venoms is not prevented by heating the venom for fifteen minutes at 100° C.. In these experiments the anticoagulant action appears rather to have been enhanced by heating, a result which is unfavourable to the hypothesis of destruction by ferment action of substances in the plasma necessary for its subsequent coagulation in the presence of calcium chloride. With other venoms anticoagulant power appears to be lost by heating. Lamb found, for example, that the anticoagulant power of cobra venom was greatly diminished by heating for thirty minutes at 75° C..

Discussion.

The early work on the venoms of Australian snakes, chiefly carried out with those of the tiger snake (*Notechis scutatus*) and black snake (*Pseudechis porphyriacus*) both of which are strongly coagulant *in vivo* and *in vitro*, has placed undue emphasis on the coagulant properties of the venoms of the Australian elapines. Of four other snakes of this group whose venoms I have so far investigated only *Pseudechis guttatus* which is closely allied to the black snake, exhibits this property. The venoms of the copper-head, death adder and of the large snake described by Kinghorn,[19] *Oxyuranus maclennani*, have no coagulant power *in vitro* or only a feeble effect in high concentrations. It is possible that if doses of copper-head and death adder venom equivalent to those effective *in vitro* were injected intravenously, corresponding activity might be revealed *in vivo*, but the importance of confirming this general principle demonstrated by Lamb in the case of *Bungarus fasciatus* is hardly sufficient to warrant the large expenditure of venom necessary even in small animals. For all practical purposes the venoms of the copper-head and death adder must be regarded as non-coagulant.

Their anticoagulant action, though demonstrable both *in vivo* and *in vitro*, is feeble in comparison with that of the cobra and unlike that of the cobra does not appear to be destroyed by heat. In *in vitro* experiments the anticoagulant action of the venom of the copper-head is more powerful than that of the death adder, a result which is in agreement with Fairley's observations on changes in the clotting times of sheep.[2]

TABLE IX.

The Effect of Heat on Death Adder and Copper-head Venom

Death Adder

Dose of Venom in Milligramme.	Clotting Time.			
	Venom Unheated.	Venom Heated 30 minutes at 60° C.	Venom Heated 30 minutes at 80° C.	Venom Heated 15 minutes at 100° C.
1·0	Partial 2 hours 20 minutes.	Not clotted in 20 hours.	Not clotted in 20 hours.	Not clotted in 20 hours
0·25	2 hours 20 minutes			
0·0625	Trace 3½ hours.			1 hour 43 minutes.
0·015625	Soft 6 hours.	5 hours 50 minutes.	57 minutes.	66 minutes.
0·00390625	1¼ hours.	2 hours 50 minutes.	34 minutes.	31 minutes.
0·0009765625	35 minutes.	55 minutes.	21½ minutes.	17 minutes.
0·000244140625	20 minutes.	21 minutes.	14½ minutes.	15½ minutes.
0·00006103515625	12½ minutes.	13½ minutes.	12 minutes	13 minutes.
0·0000152587890625	11 minutes.	11 minutes.	10 minutes.	10 minutes.
Controls	10 minutes.	11 minutes.	10 minutes.	

Copper-head.

Dose of Venom in Milligramme.	Clotting Time.			
	Venom Unheated.	Venom Heated 30 minutes at 60° C.	Venom Heated at 80° C.	Venom Heated at 100° C.
1·0	No trace of clotting in 20 hours.	No clotting in 20 hours.	No clotting in 20 hours.	No clotting in 20 hours.
0·25				
0·0625				
0·015625		20 hours.	20 hours.	
0·00390625		20 hours.	20 hours.	
0·0009765625		20 hours.	20 hours	4½ hours.
0·000244140625	Soft 5½ hours.	5½ hours.	20 hours.	Soft 1 hour 40 minutes
0·00006103515625	5½ hours.			

The experiments recorded here in which plasma treated with copper-head and death adder venoms were subsequently tested with coagulant venoms are only of a preliminary nature and bacterial proteolysis of the plasma is not excluded.

Conclusions.

1. The venoms of the copper-head and death adder in the doses used have no coagulant action *in vivo* in birds or mammals.

2. These venoms have a feebly coagulant action in high concentrations on avian and mammalian plasma *in vitro*.

3. If Lamb's technique be used, a feeble anticoagulant action with both these venoms can be demonstrated on mammalian plasma *in vitro*.

4. This anticoagulant activity is not destroyed, but rather is enhanced by heating.

5. The venoms when permitted to act in high concentrations on mammalian plasma *in vitro* impair its subsequent reaction with coagulant venoms.

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Reports of Cases.

THE SUBCUTANEOUS ADMINISTRATION OF OXYGEN.

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No claim for originality is made in describing the treatment of the two cases whose histories are given hereunder, nor can any definite opinions be expressed as regards the efficiency of the special measures employed from their effect in only two cases. My only excuse for reporting these cases is that in the second it appeared that the patients' life was saved by the subcutaneous administration of oxygen and that its dramatic effect in relieving dyspnœa and cyanosis was no less pronounced in the first patient who died apparently from toxæmia.

I have never been impressed with the benefits derived from oxygen inhalations and have generally administered it in this form under the compelling feeling that something must be done in the type of case in which it has appeared to be indicated, rather than from any feeling of confidence in its effects.

As to whether the inhalation of oxygen is so ineffective as a rule because the usual method of administration is at fault or because in the conditions in which it is generally used, some change has taken place in the alveoli of the lungs which has affected the normal interchange between the gases in the alveoli and the gases in the blood circulating in the pulmonary capillaries, I am not qualified to express any opinion of value. The fact remains that the effect of inhaled oxygen is as a rule disappointing. I am aware that oxygen has been given subcutaneously in the treatment of lobar pneumonia in a few cases, but apparently it has not been at all widely used in this manner.

Mr. C.H., aged fifty-three years, was seen on November 12, 1928, suffering from broncho-pneumonia affecting mainly the lower lobes of both lungs. His temperature was 38·9° C. (102° F.) and his respirations 24. He was admitted to the Ararat Public Hospital and was progressing apparently favourably until November 24, 1928, when his pulse became rapid and his colour cyanotic. He also became very dyspnœic and orthopnœic. Up to this time the physical signs in his chest had undergone very little change, but his temperature had gradually fallen to 37·2° C. (99° F.) in the morning and 37·8° C. (100° F.) at night. No tubercle bacilli were found in his sputum.

Oxygen was administered subcutaneously in his left axilla in sufficient quantity to raise a patch of emphysema twice the size of the palm of the hand. The effect was

noticeable in about twenty minutes. His colour became normal and the dyspnœa greatly improved. The subcutaneous emphysema had completely gone in three hours. Three injections of oxygen were given at intervals of four hours and after each injection the dyspnœa was definitely improved and the cyanosis temporarily cleared up and the patient stated he felt more comfortable. Apparently, however, the toxæmia was having an increasing effect on the myocardium, because his pulse became progressively weaker and he died on November 26, 1928. Just before death the pink colour of his lips was a striking feature.

Mrs. S.P., aged thirty years, was admitted to the Ararat Hospital on November 16, 1928, with a left basal lobar pneumonia occurring during an attack of influenza. This patient had been under treatment by me for three years for auricular fibrillation and a greatly dilated heart. She had been on digitalis constantly during this period. Three months ago it had been necessary to empty the uterus of a three months' pregnancy as she was rapidly going down hill with cardiac failure accentuated by the pregnancy. Her condition was desperate on admission to hospital, but she was kept going with the usual measures until November 26, 1928, when she appeared to be *in extremis*. She was then given oxygen injections into the axilla every four hours for three injections and the effect was dramatic. The cyanosis which had been intense, cleared extraordinarily rapidly and the very distressing dyspnœa was relieved. After the third injection she maintained the improvement. The pneumonia eventually cleared up and she was discharged from hospital on December 23, 1928. The effect of the injections in this case was so very striking that I am convinced that the patient's life was saved thereby.

In both these cases the ordinary routine treatment for pneumonia was carried out. Digitalis was given orally from admission to hospital, digitaline, pituitary extract, morphine and adrenalin were used hyperdermically when required. The oxygen was given from a cylinder through a tube attached to a "Record" syringe needle. The gas was turned on so as to come gently through the needle and the needle was introduced into the axillary subcutaneous tissue. The only risk appears to be that of injecting the gas into a blood vessel which is exceedingly remote.

It is hoped that a more general trial of this method will be made by others, so that its value may be estimated.

Reviews.

CORYZA.

SOME popular delusions are so deeply engrained as to be almost ineradicable. A typical example is that exposure to cold is the cause of coryza. The medical view, that coryza is an infectious disease, has been propounded by numerous authors in numerous works, but is not yet "understanded of the people." We now welcome another attempt to teach the truth by Professor Leonard Hill and Mr. Mark Clement.[1]

The thesis is presented at length and with ample confirmatory evidence, but unhappily in language which is sometimes stilted, sometimes slangy and not always lucid. The matter is ill-digested and ill-coordinated. Can it be that Professor Hill has given a heap of notes and articles to an assistant to put together and see through the press?

The volume opens with a chapter on anatomy and physiology, apparently addressed to the lay reader. It is excellent. There follows a fanciful one on the psychological aspect of "catching cold." We are told that "a mother mindful of her child's welfare in inclement weather wraps him up with thick vests, gloves and muffler"; that "he becomes the victim of an infantile fixation, a common cause of maladjustment to environment." "Thus the cold assumes a psycho-pathological aspect whose psychological component needs eliminating as completely as the multiplying microorganisms which overcome the resistance of a weakened host. . . . One is faced with the dual problem of effecting a psychological catharsis and a physical cure."

Another strange statement is that there is a relation between the mucous membrane of the respiratory part of the nose and the sexual organs. "There is evidence that colds occur most often on Mondays and the days following holidays. Over-eating and sexual indulgence then come into play." We had innocently supposed that it was a catarrh of a different character to which sexual libertines are prone.

Our authors supply us with ample material, full measure running over. They find room for disquisitions, not only on influenza, bronchitis, pneumonia, tuberculosis and asthma, but also on scarlet fever, infectious diarrhœa, rheumatic fever, trench feet, chill on the liver, nay even a little on cancer, yellow fever, fowl plague and gastro-enteritis of rats. They supply us with directions for the domestic installation of mercury vapour and carbon arc lamps. Sometimes it is difficult to find reasons for such divagations: in one case we succeeded; the fallacy that "chill' is the cause of consumption suggests chilblains and accordingly the article on tuberculosis is followed by one on the cause and treatment of chilblains.

The authors strongly advocate fresh air and light clothing and strongly oppose coddling, but go occasionally to extraordinary extremes, advising that boys at public schools should sleep out in the spacious grounds. "If all boys slept in the open, in addition to a big drop in the incidence of all diseases, there would be a marked increase in mental and physical agility." Perhaps this was written before the last English winter.

The chapter on prevention may be strongly recommended, so also a short one on treatment.

Despite the incoherence of much of the book, its repetitions, occasional contradictions and excesses, it contains much excellent matter and the medical man who reads it with judgement will find much good advice on hygiene, in diet, clothing, exercise, ventilation and abstemiousness.

The printing, paper and binding are very good.

[1] "Common Colds: Causes and Preventive Measures," by Leonard Hill, M.B., F.R.S., Hon. A.R.I.B.A., and Mark Clement; 1929. London: William Heinemann (Medical Books) Limited. Demy 8vo., pp. 134. Price: 7s. 6d. net.

SYMPTOMS OF DISEASE.

AN encyclopædia of symptomatology of disease, medical, surgical, gynæcological and of the various special subjects has been edited by Dr. Letheby Tidy under the title of an "Index of Symptomatology."[1] The editor has been assisted in the compilation of the work by twenty-five well known and accepted British authorities upon the articles appearing above their names. In the preface the editor states: "This book is intended to provide an account of the symptomatology of disease, the general object has been to give a reasonably full description of each disease without unduly dwelling on minor complications and variations." The editor is to be congratulated upon the excellence of the resulting work.

The diseases are arranged in alphabetical order and each article presents a clear, concise, but quite a comprehensive account of the symptoms of the disease. A fairly full supplementary index is appended which, when used in conjunction with the text, makes of the work one of differential diagnosis. The book will be welcomed by the profession generally as not only a reliable guide, but one of very ready reference.

[1] "An Index of Symptomatology," by Various Writers; Edited by H. Letheby Tidy, M.A., M.D. (Oxon.), F.R.C.P. (London); 1928. Bristol: John Wright and Sons, Limited. Royal 8ov., pp. 722, with illustrations. Price: £2 2s. net.

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The Cancer Problem.

THE public has allowed itself to be concerned in the cancer problem. In every State of Australia organized efforts have been and are being made to convince those who have riches, that if money is provided, the disease, cancer, can be conquered. The cancer campaigns have been conducted by persons recruited from many callings and occupations. It is extremely doubtful whether the majority of those making appeals, had any knowledge of the work that has been carried out in the various countries, or whether the members of the committees have any definite ideas of the problems that remain to be investigated. In nearly every instance cancer research was spoken of in intimate association with treatment. The public, influenced by the earnestness of the appeals, recognizing the fatal nature of the disease and impressed by its frequent occurrence, was incapable of discriminating between scientific investigation and the application of methods of treatment that are neither new nor likely to throw light on what is unknown.

A few weeks ago we published a learned and peculiarly clear account of the recent progress that has been made in the investigation of malignant disease by Dr. Julian Smith. In this article he has marshalled practically all the facts that have been discovered concerning the ætiology of cancer and has evolved a fascinating hypothesis, admittedly incomplete, to explain limitless overgrowth of tissue cells, the essence of malignant disease. He has found that the European workers of today accept the doctrine that growth is dependent on a chemical stimulant, that the normal processes of development of the organs and tissues of the body, of repair, of physiological hyperplasia is impossible without this chemical substance. Its nature is still unknown and no one is prepared to adduce evidence in favour of it being a single hormone-like body, not tissue-specific, although it is not suggested that there is a separate stimulin for each variety of tissue cells. The hypothesis is that under normal conditions growth continues in response to the stimulus until the physiological demands of the tissues are satisfied and the body as a whole exercises a restraining control, leading to the suspension of growth or replacement. The mechanism of this inhibition of growth remains obscure. According to the hypothesis it is when this process of inhibition breaks down, that limitless overgrowth occurs, that is malignant disease. Dr. Julian Smith also puts forward the view that embryonal cell rests are held in check by this inhibitory mechanism, but under the influence of the growth stimulating factor, in certain circumstances, these embryonal cells take on malignant hyperplasia. It will at once be apparent that there is much that has yet to be discovered before the claim can be justified that the ætiology of cancer has been established. It is still uncertain whether the carcinomata are essentially different from the sarcomata or whether the difference is merely the result of the accidental failure of growth restraint affecting epithelial structures or embryonal connective tissue. Cancer of the lower animals may be the same disease as cancer of human beings; the clinical and pathological difference may be due to variations inherent in the animal concerned. But there is no justification at the present time to assert that mouse or chicken neoplasms are identical with human carcinoma or sarcoma. The hypothesis may be regarded as the most acceptable explanation yet offered, since it is supported by much experimental evidence. But it is still unproven. Until the whole story is complete, it is futile to dogmatize in regard either to treatment or to prevention. Australian investigators should join with the vast army of searchers in Europe and America and endeavour to add one or two fresh facts to our store of knowledge of the malignant disease.

Dr. Julian Smith is equally interesting when he deals with the researches conducted in connexion with the effect of X and γ rays on normal and on malignant cells. The knowledge to be gained by accurate observation of tissues subjected to the influence of varying kinds of radiation is very

important. It must, however, be pointed out that the treatment of a malignant tumour in a human being by radium, X rays or other physical agent, unless associated with histological or bio-chemical control, has nothing whatsoever to do with cancer research and will not lead to any advancement in our knowledge of cancer. The effects on the patient and on the tumour of these agents are known and even if it were not so, the small population of Australia as compared with that of Europe or America imposes a limit to the usefulness of observations in the Commonwealth. Cancer research is part of medical research. Serious inquiry, patient investigation, coordinated effort and freedom from outside control are essential. Research should be divorced from treatment. The public should be discouraged from anticipating a sensational discovery; no one should waste his time in seeking for a cure of cancer until the nature of the disease is fully understood.

Current Comment.

THE PITUITARY HORMONES.

WHEN Starling postulated the existence of chemical substances in the internal secretion of the ductless glands which act as chemical messengers to stimulate various organs to carry out their functions, he indicated that this physiological process was a highly complex one. Since those days an immense amount of work has been carried out and many facts have been elucidated. In spite of this work, the nature of Starling's chemical messengers is just as obscure today as it was a quarter of a century ago. There is one grave difficulty in connexion with this subject. Hormones, like enzymes, seem to have a biological existence. Whether they are chemical substances, capable of analysis, or whether they are functions of complex organic substances in which certain side chains assume a particular molecular arrangement cannot be decided until much more information is available. In view of this uncertainty concerning the production of the biological functions spoken of as hormonic function, it is obviously necessary to adopt biological methods for the purpose of recognizing the presence of the active principle in any organ extract. It is true that thyroxin has been synthesized and its quantity can be determined by an estimation of its iodine content. But it is probable that the actual active principle of thyreoid gland resides in the iodine containing substance which has other chemical properties. It follows that in discussions on whether the glands of internal secretion have single or multiple active principles it would be wise at present to speak of distinct functions of a single secretion which may be separated by separating the constituents of the secretion. Hitherto, although several competent bio-chemists have postulated more than one active principle in some of the glandular secretions, evidence of the independence of such active principles has not been established. It appears that Oliver Kamm, a bio-chemist working in the research laboratories of the great firm of Parke, Davis and Company at Detroit, has succeeded in proving beyond doubt that the posterior lobe of the pituitary gland produces at least two definite hormones. His work has already received recognition in the United States of America. He has been awarded the $1,000 prize of the American Association for the Advancement of Science for the most noteworthy contribution to science presented at the annual meeting.

It has long been known that pituitary gland extract exerts an action on the pregnant uterus leading to a contraction of the muscle, raises blood pressure by contracting the peripheral vessels and reduces the amount of urine secreted by the kidneys. The first or oxytocic action is gauged by comparing the contraction of strips of the uterine muscle of a pregnant guinea-pig immersed in Locke's solution to which is added some of the pituitary extract with the contraction of the same muscle immersed in plain Locke's solution. The second action is determined by direct measurements of the blood pressure of dogs to whom the extract is administered usually by intravenous or intraperitoneal injection. The effect of the extract on the secretion of urine is measured by collecting the bladder urine of rabbits after the subcutaneous injection of the extract and comparing the rate of flow with that of the same animal before the injection. Kamm and his colleagues have published the details of their experimental work in a series of papers.[1] It is not our intention to reproduce the details of the experiments in this place. The reader interested in physiological investigations will seek the information in the original papers. The first matter of importance in Kamm's work was the determination of the optimum acidity of the extracting fluid. Briefly, he found that when the gland is extracted in a fluid with a hydrogen ion concentration of approximately six, there is a greater loss of pressor activity than of oxytocic activity. The glands are desiccated in acetone within a few minutes of the death of the animal. This process does not interfere with the activities of the extract. An extract is then made of the dried powder in 0·25% acetic acid and this is heated to 95° C. for thirty minutes, cooled and filtered. The residue is extracted in acetic acid as

[1] O. Kamm, T. B. Aldrich, I. W. Grote, L. W. Rowe and E. P. Bugbee, *The Journal of the American Chemical Society*, February 4, 1928, page 573; L. W. Rowe, *Endocrinology*, September-October, 1928, page 663; E. P. Bugbee, *Endocrinology*, September-October, 1928, page 671; O. Kamm, *Science*, February 17, 1928, page 199; O. Kamm, Transactions of the American Association for the Advancement of Science (meeting on December 28, 1928, summary kindly supplied by the author).

before and the filtrates combined. The filtrate is then concentrated at a low temperature and the proteid material salted out with ammonium sulphate. The precipitate is then extracted in glacial acetic acid; the extract is treated with petroleum ether and the resulting precipitate washed with ether and dried. This dried product contains practically all the active material of the fresh gland. Kamm has devised a method of separating the oxytocic from the pressor fraction. He dissolves the dried substance in glacial acetic acid at 40° C. and reprecipitates with sulphuric ether. This process is repeated. A clear solution in water is then treated with petroleum ether. A gummy precipitate forms which has been found to contain nearly half of the oxytocic activity, while the whole of the pressor activity and the remainder of the oxytocic remain in solution. By a careful process of fractionation seven preparations were obtained, some exercising relatively little pressor activity and much oxytocic activity, others containing little of the substance that gives rise to oxytocic activity and yet others that produce small physiological effects. Further experiment enabled Kamm to concentrate the pressor principle and to reach a relatively high separation of the two principles. In order to demonstrate that all these chemical manipulations and treatments had not merely destroyed some substance contained in the extract, he combined all his fractions and accounted for practically all the original activity. In regard to the action on the secretion of water in the urine, it appears that this is a property of what Kamm calls β hypophamine, the fraction that contains the pressor hormone. He points out, however, that this hormone controls the utilization of water by all the tissues of the body.

It is a remarkable thing that the pituitary gland should produce a secretion, one constituent of which exerts a powerful contractile action on the uterine muscle in pregnancy and that this substance should remain physiologically active after having been treated with glacial and dilute acetic acid, petroleum ether, sulphuric ether and various inorganic salts and after having been heated, dried and dissolved several times. It is said to be stable and the manner of its preparation would indicate that it must be extremely stable. In powder form it contains admixed with it about 3% to 4% of pressor principle. Kamm speculates in regard to its constitution. In the first place the behaviour of both the oxytocic and the pressor hormones towards dialysis suggests that the molecular weight is in the neighbourhood of six hundred. Acting on this assumption, he proceeded to deal with the fractionation as if the hormones were much simpler than protein bodies. Whether he is right or not remains undecided. He has expressed the opinion that there is little chemical difference between the two active principles, that both are basic bodies, probably amines. Nothing is yet known concerning the chemical structure of any hormone. If the pituitary hormones exist independently of globulins, as appears from Kamm's work to be the case, it may transpire that they actually exist as chemical bodies and not merely as functions of a known chemical substance. Be this as it may, the work of Kamm has proceeded much farther than any work previously recorded in this connexion. It is too early to consider the effect of this work on the therapeutic application of the hormones, but its real significance lies in the enlightenment of a hitherto obscure physiological process.

THE PAN-PACIFIC SURGICAL CONFERENCE.

THE Pan-Pacific Surgical Conference is to be held under the auspices of the Pan-Pacific Union from August 14 to 24, 1929, at Honolulu, Hawaii. The conference will be organized by Hawaian committees under the general chairmanship of Dr. Nils P. Larsen and by Pacific Coast States and British Columbian committees under the chairmanship of Dr. George W. Swift. There will be sixteen sections whose programmes are entirely American. It is stated that several symposia will be prepared, but from the preliminary details available, it is not quite certain whether the term symposium is employed in the sense of a collection of articles by various authors on the same subject. It appears that invitations have been sent to many countries by the Director of the Pan-Pacific Union through the usual diplomatic channels. In the letter of invitation it is pointed out that ten delegates from each Pacific country will be housed and entertained by the committee in Hawaii.

We learn that Dr. Larsen issued a very pressing invitation to Australasian surgeons through the College of Surgeons of Australasia to be present at the conference in August and to participate in the deliberations. The suggestion has been made that some of the American surgeons attending the conference should proceed to Australia after its termination and should visit the several States of the Commonwealth and the Dominion of New Zealand. The objects of the conference are set out in the following terms: (i) To bring together surgeons from countries bordering on the Pacific; (ii) to permit the exchange of surgical ideas and methods; to develope an "acquaintanceship among the surgeons" meeting on a common ground so that they may be instrumental in developing a spirit of good fellowship among the races represented at the conference.

The subjects to be discussed include craniocerebral injuries, brain tumours, ramisection, cleft palate, nasal reformation and other forms of facial plastic work, goître, the surgery of the thorax, including thoracoplasty, gall bladder infections, intestinal surgery, gastric ulcer, anæsthesia for abdominal operations, spinal and regional anæsthesia, the technique of hernia operations, blood transfusion, rectal surgery, fractures, tuberculosis of bones, the treatment of cataract, mastoiditis, sinusitis and affections of the larynx. Leprosy will also be discussed. Dr. M. T. McEachern will open a debate on hospital standardization.

Abstracts from Current Medical Literature.

MORBID ANATOMY.

Sprue.

F. P. MACKIE AND N. HAMILTON FAIRLEY (*The Indian Journal of Medical Research, January*, 1929) have summarized their findings in eight autopsies on the bodies of persons who died from sprue. The mucous membrane of the tongue is thinned and atrophic and the lingual papillæ may disappear. There is desquamation of the epithelial layers and occasionally loss of tissue amounting to superficial ulceration with little sign of inflammatory reaction. The mucous membrane of the intestine is atrophied and thinned. Degeneration of the epithelium occurs and proceeds to such a stage that the epithelium almost completely disappears. There are no signs of inflammatory reaction. There was an invasion of bacteria deep into the mucosa; the invasion takes place *ante mortem*. In some instances the liver was normal, in others there were fatty change, cloudy swelling and disintegration of the parenchyma. There was no overgrowth of interstitial tissue and no change in the Kupffer cells or in Glisson's capsule. There was in two instances a specific atrophy of cardiac muscle out of all proportion to any decrease explicable in terms of mere starvation. Microscopical changes of a degenerative nature such as might be induced by the action of a toxin, were found occasionally in the liver, kidney and adrenals. Iron pigment was laid down in moderate amount, especially in the liver, but not in the same quantities as characterize pernicious anæmia. Aplasia was found in most instances in the bone marrow of the femur and tibia. Red marrow, when present, was much reduced in quantity. In two instances, however, there was extensive hyperplasia, similar to that seen in pernicious anæmia. The findings suggest to the authors that there may be two distinct ætiological factors in the production of the sprue syndrome—a specific virus, acting on the intestinal tract and resulting in degeneration, atrophy and diminished resistance of the mucosa to microbic invasion, and secondary bacterial invaders and their soluble toxins which give rise to a chronic toxæmia resulting in further atrophy of the cells of the parenchyma in the viscera and of the erythroblastic tissue in the bone marrow. The toxin may primarily stimulate and later lead to exhaustion of the hæmopoietic function so that in the end almost complete aplasia results. The authors thus believe that "sprue is primarily a disease of the intestinal tract which, if progressive, results ultimately in degeneration and destruction of the absorbing and secretory tissues and the production of slow progressive starvation. The absorption of toxins from the damaged mucosa perhaps associated with actual bacterial invasion, appears to be an important factor in the progressive anæmia and other late manifestations of the disease."

Chronic Appendicitis.

T. BHASKARA MENON (*The Indian Journal of Medical Research*, January, 1929) states that in a cross section of a normal appendix there are on an average about six lymph follicles and three well defined germ centres. No pronounced involuntary atrophy of the lymphoid tissue of the appendix occurs with age between the ages of ten and fifty. In a chronically inflamed appendix there is a tendency for atrophy of the lymphoid tissue to occur. There seems to be a definite relationship between lymphoid hyperplasia of the appendix in children as well as adults and colicky pain in the lower part of the abdomen. The occurrence of eosinophilia in the mucous membrane of the appendix is a normal phenomenon, at any rate in the tropics. Eosinophile infiltration of the submucosa of the appendix is evidence of chronic appendicitis.

Glycolytic Action of Some Tumours.

IF a section of a tumour be placed in Ringer's solution containing glucose and nitrogen and kept in a water bath at 38° C., glycolysis occurs and lactic acid is formed. S. L. Baker, F. Dickens and E. J. Gallimore have carried out some experiments of this nature (*The British Journal of Experimental Pathology*, February, 1929). They used Jensen rat sarcoma and Rous chicken sarcoma. Lactic acid determinations were made by the modification of Friedmann, Cotonio and Shaffer and glucose estimations were made by the method of Folin and Wu. The experiments were carried out under anaerobic conditions. It was found that there was a great difference between normal tissues and the malignant tumours as far as the anaerobic metabolism of glucose was concerned, the tumour tissues producing from five to ten times as much lactic acid as the normal tissues. The amount of lactic acid produced was nearly equal to the amount of glucose destroyed. The addition of "Insulin" or thyroxin produced no demonstrable effect upon the glucose metabolism.

Primary Carcinoma of the Fallopian Tube.

ERNEST SCOTT AND MARGUERITE G. OLIVER (*The Journal of Laboratory and Clinical Medicine*, February, 1929) report two cases of primary carcinoma of the Fallopian tube. They have found records of one hundred and ninety-nine similar cases in the literature. The microscopical picture is usually that of a papillary alveolar carcinoma. In the two cases reported the tumour was of this nature. In neither instance was a diagnosis made prior to operation. The gross appearance is often deceiving and the presence of a malignant growth may be overlooked if a careful routine microscopical examination is not made.

Trauma and Tumours.

LEILA CHARLTON KNOX (*Archives of Pathology*, February, 1929) writes a critical review of the question of the relationship of trauma to the production of neoplasms. She also discusses the award of compensation for trauma alleged to have caused a tumour. In dealing with the first of these aspects the author presents a *résumé* of the more important literature and concludes that a causative relationship between the two has never been completely established. She cites a few examples which suggest the possibility that a single trauma may induce a tumour, but she points out that proof even in these few instances is lacking. She holds that the causative relationship cannot be established until it is demonstrated by experimental methods that a single injury can regularly produce a tumour. In regard to the second aspect of her communication, that of compensation, the author states that it is unjustifiable to award compensation on the basis of the production of a tumour following a single trauma. If proof of an injury is received and the presence of a tumour is determined by microscopical examination, it may be justifiable to award compensation on the grounds that trauma has acted as a collateral or adjuvant agent by causing chronic irritation or has determined a metastatic site for a cancer already present in the body or has stimulated a growth to greater activity. In many of the instances in which compensation has been granted, the trauma has merely called attention to a pre-existing tumour. In these circumstances there is no valid basis for compensation.

The Grading of Carcinoma of the Rectum.

F. W. STEWART AND J. W. SPIES (*The American Journal of Pathology*, March, 1929) have investigated the grading of rectal carcinomata according to the method of Broders and have come to the conclusion that this method is of value in estimating the probable course of the disease. Most of the tumours in their series had received palliative radiation. In many instances more than one specimen was removed for microscopical examination. In Grade I they placed tumours with malignant features, but with a structure approaching that of benign adenoma. In these the epithelial cells lined distinct glandular cavities. The percentage of tumours in this group was eleven. In Grade II the tumour cells lined definite glandular cavities, the cavities were more irregular and there was a definite tendency towards the production of papillary ingrowths and outpocketings of varying sizes and shapes. The percentage of tumours in this group was 56. Tumours in Grade III had in addition solid areas in which glandular tendencies were either lost or were represented by

abortive attempts at tubule formation. The percentage of tumours in this group was 24. Grade IV comprised a heterogeneous group of tumours. These manifested various structures ranging between adeno-carcinoma and diffuse carcinoma. The percentage in this group was nine. In connexion with each group the authors give details of the microscopical appearances. The average duration of symptoms prior to application for treatment was twenty months in Grade I, eleven and ten months in Grades II and III and six months in Grade IV. The duration of the disease was difficult to determine. In Grade I the duration was approximately seventy months, in Grade II thirty months, in Grade III twenty-one months and in Grade IV ten months. It is the tendency of a tumour of the rectum to maintain its type locally, rather than to develope more malignant features. At the same time one or two instances were noted in which the grade was changed. The authors emphasize the fact that they are dealing only with superficial biopsy material. Their findings encourage them in the belief that the lower grades of colloid carcinoma may run a very slow, relatively benign course and that surgery may be of value in this group, even when tumours are recurrent.

MORPHOLOGY.

Parthenogenesis in the Dog.

SO-CALLED parthenogenesis in the ovary of the dog has been studied by Otto F. Kampmeier (*American Journal of Anatomy*, January 15, 1929). In this mammal the number of atretic follicles undergoes periodic variation relative to the œstrous cycle, the degenerative process reaching a maximum some time after ovulation, when the ovary contains later stages of *corpora lutea*. The prominent features of atresia are the formation of a hyaline band external to the *membrane granulosa* and degeneration of the follicular epithelium, followed by replacement of the follicle by mesenchymatous tissue. Ova of the degenerate follicles evince various forms of regression; the majority is characterized by vacuolated or granular cytoplasm with pyknotic, vacuolated or fragmented nuclei; occasional ova are invaded by phagocytes. Comparatively few ova exhibit characteristics of parthenogenesis, either in the peripheral situation of the nucleus, associated with maturation, or in the fragmentation (irregular segmentation) of the cytoplasm, some portions of which may be binucleate, others non-nucleate. Of the more symmetrical fragmentations two are more prevalent than three and four cell stages, but stages of eight to ten blastomeres were observed three times and masses interpreted as morulæ twice. Polyovular follicles are of frequent occurrence in ovaries of some dogs, where a single follicle may contain as many as eleven ova. The author holds the view that oogonia in close contact in these follicles may have been mistaken for a segmenting ovum by some workers. He discusses the work, based chiefly upon ovaries of the mouse, rat, guinea-pig and rabbit, of previous authors who all agree that some form of segmentation occurs in atretic follicles and he is of the opinion that the fault lies in the uses of the term parthenogenesis. If used loosely to designate any division of the fertilized ovum, parthenogenesis is of frequent occurrence; for this process he suggests the term "pseudoparthenogenesis." If it is taken to mean regular cleavage and development, evidence is lacking in the ovaries of the dog.

Mitochondria.

E. S. Horning (*Australian Journal of Experimental Biology and Medical Science*, March 16, 1929) reviews the recent literature dealing with the mitochondrial problem and discusses the apparent function and behaviour of mitochondria within the animal and plant cell. The arrangement of these bodies around the periphery and nucleus of the cell appears to be a surface tension phenomenon dependent upon their phosphatide components and the differences in the orientation of mitochondria in the surface cytoplasm of infusorians may be correlated with the presence and proximity of the myoneme threads. The general behaviour of these cell components during cellular metabolism appears to lend considerable support to an enzymatic conception of mitochondrial activity.

The Effect of Low Temperature on Mitosis in Vitro.

F. G. SPEAR (*Archiv für experimentelle Zellforschung, Band* VII, *Numero* 4) states that the early work on the effect of temperature on growth and division has been limited until recently to observations upon vegetable cells and the segmentation of the fertilized ovum. With the introduction of the technique of tissue culture *in vitro* observations became possible on a great variety of tissues with the further advantage that the reaction of individual cells to various stimuli could be examined without the modification of behaviour consequent upon the action of nerve or blood supply. Using tissues obtained from the chorioid and sclerotic of chick embryos of seven to eight days' incubation, the author made cultures in fowl plasma and chick embryo extract. After subculturing and incubating for eighteen to twenty-four hours, he selected cultures as controls and exposed others for various periods to low temperatures. The duration of mitosis in chick tissues at 38° C. varies from twenty-three to sixty-five minutes. At 28° C. the process takes about twice as long and at lower temperatures it is still further delayed or arrested altogether. If, however, cultures are placed in a cold room at 0·5° C. for four hours and then reincubated at 37° C., examination after five and a half hours reveals as many mitotic figures as in controls. Further examination reveals that after eleven hours' incubation the number of mitoses actually exceeds that observed in controls. Apparently this increase approximately compensates for the diminution seen during the first five and a half hours' incubation subsequent to chilling.

Embryonic and Glandular Extracts and Mouse Sarcoma.

E. S. HORNING AND J. M. BYRNE (*Australian Journal of Experimental Biology and Medical Science*, March 16, 1929) made cultures of mouse sarcoma (37c) in a medium of fowl plasma and various glandular extracts. They point out that the work of recent authors together with their own investigation has successfully shown that the growth of cells, cultivated *in vitro*, remains constant in an unchanging nutrient medium and varies with modification in the composition of the medium. In the authors' experiments it was found that the proliferation *in vitro* of the mouse sarcoma was more active in a medium of testicular extract taken from sarcomatous mice than in a medium composed of testicular extract from healthy normal mice; similarly it was shown that embryonic juice does not so readily induce cell multiplication as tumour extract. The general cytology of the sarcoma cultures is described. The origin and nature of the pseudofibroblasts and clasmatocytes is discussed and the authors conclude that the former cell type is merely a morphological variation of the malignant cells which are spherical or oval in shape. The evidence in hand at present suggests that the clasmatocytes are stromal in origin.

Spermatogenesis of the Guinea-Pig.

J. BRONTE GATENBY AND SYLVIA WIGODER (*Proceedings of the Royal Society*, Series B, Volume CIV, 1929, Number 73) contend that the specific effect of X radiation on cell mitosis is due to the temporary breaking down of certain lipoid substances necessary for mitosis. They further suggest that this lipoid substance is located in the cortex of the sphere (Golgi apparatus) and that after X radiation the Golgi lipoid cortex becomes flocculent and granular. They also demonstrated that the radio-sensitive period is prior to the prophase and that the cell at this period is in a state in which recovery from the effects of broken down lipoids is impossible, so that an abnormal mitosis leading to the death of the cell is the final result. Thereby assuming that X radiation does alter the lipoid cortex of the Golgi material, they conclude that cells entering mitosis might be killed by the inability of the centrosomes to pass out of the idiozome preparatory to amphiaster formation. During this investigation these workers found no evidence for the theory that the centrosome is radio-sensitive, but that on the other hand post nuclear bodies are sometimes abnormal in testes which have been radiated.

Medical Societies.

THE MEDICAL SCIENCES CLUB OF SOUTH AUSTRALIA.

A MEETING OF THE MEDICAL SCIENCES CLUB OF SOUTH AUSTRALIA was held at the University of Adelaide on December 7, 1928.

The Life Cycle of Aphis.

DR. J. DAVIDSON, Entomologist at the Waite Agricultural Institute, read a paper entitled: "The Occurrence of Sexual and Parthenogenetic Phases in the Life Cycle of Aphides." He referred to the biology of one species of *aphis*. In Australia there was only one species and that had been introduced. In America there were many species. Introduction of flowering plants was an important factor in their development. *Aphides* might be classified roughly into two groups. The life cycles were simple. The egg was laid in the autumn by sexual females and hatched in the spring to a parthenogenetic female (stem mother) which in turn gave rise to some 110 living young. In ten to fourteen days these gave rise in turn to a further batch of parthenogenetic young. When autumn again recurred these produced, not their like, but males and females.

This phase might be delayed by maintaining temperature and food supply. In some climates these parthenogenetic forms might survive to the next spring. Experimentally Dr. Davidson had kept these types for three years. So in suitable climates both egg form and parthenogenetic forms might coexist throughout years. This was true for the non-migrating form living on woody trees. The migrating form had, however, developed largely in connexion with the development of herbaceous plants. The primary host for the egg and stem mother was the woody tree, while the migratory forms went to herbaceous plants and existed in apterous parthenogenetic form, remigrating as male and female to the primary host, having also become apterous (namely, at the end of extension upon the intermediate host).

The object of the experiment was to attempt to upset the phases of development. The prolongation of the parthenogenetic phase could easily be done by keeping the temperature and food favourable. The reverse alteration was not so easy. If parthenogenetic phase were prolonged, sexual forms failed to appear after the month of May (in England). They again appeared, however, in October (normal). The sexual phase could be suppressed after its establishment under the influence of higher temperature and light. In order to test the effect of shortening of light and temperature in summer, experiments were made giving the plant only eight hours' daylight. Sexual forms appeared in June and were produced throughout the period. Two to three weeks after this darkening, some were again subjected to normal light and the sexual form did not come on until October. After these forms appeared artificial light application again reversed the order to parthenogenesis.

The result was due to light and temperature. The true sexual females were winged and so it was difficult in infecting plants not to include an odd sex female—a fact making experimentation difficult. It was suggested that chromosomal differences were responsible for these phases. Morgan had shown it to be so in *Filaphis*. In parthenogenesis there was no reduction division, while in sexual types the normal reduction giving *XX* and *XY* chromosome combinations occurred. The appearance of sex forms in October despite the temperature conditions indicated the operation of another factor than temperature or light.

Correspondence.

ANTINEURITIC VITAMIN.

SIR: Supplementary to my address on "Food Deficiency Diseases: Their Causes and Prevention," THE MEDICAL JOURNAL OF AUSTRALIA, November 29, 1928, I found recently on visiting the Medical Research Laboratories at Weltevreden, Batavia, Java, that the anti-beri beri vitamin had been isolated from the cortex of rice by Drs. Jansen and Donath. The Director, Dr. Borgh, who introduced me to Dr. Donath, assured me that this brilliant accomplishment was the result of nine years' continuous research on beri beri, following the original findings of Eijkman. Dr. Jansen, now the Director of Tropical Medicine and Hygiene at The Hague, and Dr. Donath have isolated as crystals the actual vitamin which is preventive of and a cure for beri beri.

Dr. Donath showed me hundreds of small birds in various stages of beri beri induced by feeding on hulled rice for a fortnight. Previously Eijkman's experimental work in Batavia in the production of beri beri in fowls and pigeons required a period of six months. In the laboratory there were small birds under treatment with the anti-beri beri vitamin. A thousandth part of a milligramme per day of the anti-beri beri vitamin prevented beri beri in these birds.

The anti-beri beri vitamin has been put up in infinitesmal quantities in tablet form by a somewhat elaborate process with a special *Kieselguhr*, similar to Fuller's earth.[1]

The original Dutch monograph which was translated into English and published at the end of 1927, has not yet, as far as I know, been noted in the English or American medical journals. I left some of the tablets and the monograph with Dr. Vernon at Thursday Island, where there were cases of beri beri at the hospital. In Singapore and Kuala Lumpur the work of Drs. Jansen and Donath was known, the tablets being now in regular use.

On visiting Manila six years ago I found the Philippino Health Service, both in hospital and in their health centres, used Tiki-Tiki, an alcoholic decoction from the cortex of rice, as a preventive and remedy in the treatment of beri beri. This further research of the two Dutch investigators has placed the prevention and treatment of this disease on a satisfactory basis.

Yours, etc.,

J. S. PURDY,

Metropolitan Medical Officer of Health.

Sydney,
April 2, 1929.

INFANT MORTALITY.

SIR: Might I correct the statement of Dr. Kempson Maddox in his letter, published in your issue of fourth instant, to the effect that "Sydney has the unenviable record of the highest infantile mortality of any city in Australia for the last twenty years"?

Melbourne is the only city strictly comparable for statistical purposes with the metropolitan district of this State. The other cities of Australia have comparatively small populations and are in consequence free from many of the conditions—congestion, overcrowding *et cetera*—which are so detrimental to infant life.

For the past twenty years the infant mortality rate of Sydney has been definitely lower than that of Melbourne; the same can be said for Sydney when compared with Hobart.

Further, the reduction of the infant mortality rate of Sydney has been very marked during the period under review. Comparing the quinquennial period 1908-12 with that of 1923-27 there has been a reduction of the infant mortality rate of almost 25%.

The death rate from "diarrhœa and enteritis" for the same periods has been reduced by more than 50%.

Much of the credit for this improvement is due, in my opinion, to the activities of the baby health centres which strenuously advocate the necessity for breast feeding.

[1] *Kieselguhr* is a fine powder consisting of dead infusoria, chiefly Gallionella, Melosira, Navicula, Synedra and Gomphonema. Fuller's earth powder is a china clay containing traces of iron and magnesia. There is, therefore, no similarity between the two.—EDITOR.

It has been found that the baby health centres in the metropolitan district are attended by at least 70% of the babies in the areas served by the centres. In certain suburbs the proportion is as high as 90%.

The 30% of the babies who do not attend the centres contribute more than 80% of the total "enteritis" cases treated annually in the Royal Alexandra Hospital for Children, The Renwick Hospital for Infants and the Lady Edeline Hospital for Babies (Vaucluse).

I agree entirely with Dr. Maddox's statement that "it is almost criminal to take a baby off the breast in summer (one might add 'or at any other time') except for very good reasons."

The universal support of this attitude by the medical profession would reduce the infant mortality rate still further and would achieve the desired improvement in the shortest possible time.

Yours, etc.,

E. SYDNEY MORRIS,

Director of Maternal and Baby Welfare.

Sydney,
May 9, 1929.

Obituary.

FREDERIC DOUGAN BIRD.

WE regret to announce the death of Dr. Frederic Dougan Bird which occurred in Melbourne on May 29, 1929.

Congress Notes.

AUSTRALASIAN MEDICAL CONGRESS (BRITISH MEDICAL ASSOCIATION).

THE following is based on information received from the Executive Committee of the third session of the Australasian Medical Congress (British Medical Association), Sydney, 1929.

Membership.

The first week of June has arrived and the organizers of the session are looking at the lists of those who have applied for membership with some disappointment. In three months' time the session will have begun. We appeal earnestly to members of the several Branches of the British Medical Association in Australia and New Zealand to remember that a very large amount of energy is being expended to make the third session a great success. The labours of the organizers will be fruitless unless the membership is large. Join at once and make your arrangements to attend at a later date! Up to date but 318 have applied for membership. The applications from New South Wales number 201, from New Zealand twelve, from Queensland nine, from South Australia nineteen, from Tasmania four, from Victoria 66 and from Western Australia seven.

The Section of Obstetrics and Gynæcology.

The honorary secretary of the Section of Obstetrics and Gynæcology, Dr. A. J. Gibson, of 143, Macquarie Street, Sydney, intimates that he would like to hear as soon as possible from any member who proposes to read a paper at a meeting of this section. Many papers have been promised and a large part of the programme has already been arranged. To enable him to admit as many papers as can be read within the allotted time, it is essential that early notice be received.

The Section of Anæsthetics.

There was no section of anæsthetics in any of the previous congresses held in Australia. At the third session there will be a section devoted to anæsthetics. Papers on anæsthesia in cardiac and pulmonary conditions, gas and oxygen anæsthesia in abdominal surgery, endotracheal anæsthesia and the impurities of ether among others have been offered. It is hoped that members who have experience of the employment of the newer anæsthetics, such as ethylene, will contribute papers. The honorary secretary, Dr. J. G. Hunter, of 185, Macquarie Street, Sydney, will be pleased to hear from any member who is willing to read a paper on some matters relating to anæsthesia.

Golf Competition.

A sports committee has been formed by the Executive Committee of the third session of Congress. The committee has as its members Dr. R. Gordon Craig, Dr. P. Sydney Jones, Dr. Cyril Shepherd and Dr. C. Nigel Smith. The committee will arrange a golf competition for members during Congress week. Dr. T. G. Wilson, of Adelaide, has had the generosity to offer a cup for this purpose. The details of the competition will be published at an early date.

Travelling Concessions.

The Union Steamship Company of New Zealand, Limited, advises that a reduction of 10% from the fares of duly accredited members and their wives if travelling with them will be granted. The Associated Steamship Owners, embracing Huddart, Parker, Limited, Australasian United Steam Navigation Company, Limited, Melbourne Steamship Company, Limited, Adelaide Steamship Company, Limited, and McIlwraith, McEacharn, Limited, announce that a concession reduction of 10% will be allowed from the fares of members and their wives and lady relatives travelling with them. The reductions allowed by Huddart, Parker, Limited, in respect of lady relatives has application only in connexion with travel by steamers on the Australian coast. It does not apply to travel by steamers to or from New Zealand.

Medical Prizes.

THE GARTON PRIZE.

THE British Empire Cancer Campaign announces that a prize and medal known as the Garton Prize and Medal will be awarded to the author or authors of the best essay on the early diagnosis of cancer submitted. The medal will be accompanied by a prize of five hundred pounds. If several essays of sufficient merit are received, the council may divide the prize or make additional awards. If no essay of sufficient merit be received, the council may reserve the prize.

The essays must be printed or typewritten in English. They must represent the results of original investigations undertaken either wholly or in part during the three years immediately preceding the year in which the prize shall be awarded. The essays are to bear mottoes or devices, but not the names and addresses of the authors. The latter are to be enclosed in sealed envelopes bearing the same mottoes or devices as the essays. The essays must be received by the honorary secretary of the British Empire Cancer Campaign, 19, Berkeley Street, London, W.1, not later than December 31, 1931.

PUBLIC MEDICAL OFFICERS' ASSOCIATION OF NEW SOUTH WALES.

THE Honorary Secretary of the Public Medical Officers' Association of New South Wales has forwarded to this journal a copy of a letter which has been addressed to public medical officers. A conference of medical officers "employed by statutory public authorities" in Australia will be held at Sydney during the week September 2 to September 7, 1929, at the time of the meeting of the third session of the Australasian Medical Congress (British

Medical Association). A general meeting will be held on September 2 and this will be followed at convenient times by meetings of delegates, representative of public medical officers in the several States. The object of the conference is to secure cooperation in endeavours to improve the efficiency, status and remuneration of public medical officers in Australia. Further information on the subject may be obtained from Dr. H. Hastings Willis, Middle Harbour, Chatswood, New South Wales.

Books Received.

A GRAPHIC GUIDE TO ELEMENTARY SURGERY, by Prof. Dr. Th. Naegeli, Translated by J. Snowman, M.D., M.R.C.P., with an Introduction by Dr. C. Garré; 1929. London: John Bale, Sons and Danielsson, Limited. Royal 8vo., pp. 205. Price: 12s. 6d. net.

QUAIN'S ELEMENTS OF ANATOMY: Edited by Thomas Hastie Bryce, M.A., M.D., F.R.S., and Thomas Walmsley, M.D.; Eleventh Edition; Volume IV, Part III: The Heart; 1929. London: Longmans, Green and Company. Royal 8vo., pp. 160, with illustrations.

THE PRACTICAL MEDICINE SERIES, COMPRISING EIGHT VOLUMES ON THE YEAR'S PROGRESS IN MEDICINE AND SURGERY: Dermatology and Syphilis. Edited by William Allen Pusey, A.M., M.D., and Francis Eugene Senear, B.S., M.D., with the collaboration of Max S. Wien, M.D.; Urology, edited by John H. Cunningham, M.D.; 1928. Chicago: The Year Book Publishers. Crown 8vo., pp. 423, with illustrations. Price: $2.25 net.

ARTHRITIS AND RHEUMATOID CONDITIONS: THEIR NATURE AND TREATMENT, by Ralph Pemberton, M.S., M.D.; 1929. Lea and Febiger. Royal 8vo., pp. 354, with illustrations. Price: $5.00 net.

Diary for the Month.

JUNE 11.—Tasmanian Branch, B.M.A.: Branch.
JUNE 11.—New South Wales Branch, B.M.A.: Ethics Committee.
JUNE 12.—Central Northern Medical Association, New South Wales.
JUNE 13.—New South Wales Branch, B.M.A.: Clinical Meeting.
JUNE 13.—Victorian Branch, B.M.A.: Council.
JUNE 14.—Queensland Branch, B.M.A.: Council.
JUNE 18.—Tasmanian Branch, B.M.A.: Council.
JUNE 18.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
JUNE 18.—New South Wales Branch, B.M.A. Organization and Science Committee.
JUNE 18.—New South Wales Branch, B.M.A.: Medical Politics Committee.
JUNE 19.—Western Australian Branch, B.M.A.: Branch.
JUNE 19.—South Sydney Medical Association, New South Wales.
JUNE 19.—Section of Obstetrics and Gynæcology, New South Wales Branch, B.M.A.
JUNE 26.—Victorian Branch, B.M.A.: Council.
JUNE 27.—New South Wales Branch, B.M.A.: Branch.
JUNE 27.—South Australian Branch, B.M.A.: Branch.
JUNE 28.—Queensland Branch, B.M.A.: Council.

Medical Appointments.

Dr. Ellen Maude Wood (B.M.A.) has been appointed Government Medical Officer at Dora Creek, New South Wales.

* * *

Dr. Gerald R. Fetherston (B.M.A.) has been appointed Resident Radiologist to the Newcastle Hospital, New South Wales.

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser," page xx.

MAREEBA DISTRICT HOSPITAL: Medical Superintendent.
ST. MARGARET'S HOSPITAL, SYDNEY: Resident House Surgeon.
SYDNEY HOSPITAL, SYDNEY: Honorary Relieving Assistant Physician.
THE BRISBANE AND SOUTH COAST HOSPITALS BOARD: Consulting Electrologist.

Medical Appointments: Important Notice.

MEDICAL practitioners are requested not to apply for any appointment referred to in the following table, without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCH.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 30 - 34, Elizabeth Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company, Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. Building, Adelaide Street, Brisbane.	Members accepting appointments as medical officers of country hospitals in Queensland are advised to submit a copy of their agreement to the Council before signing. Brisbane United Friendly Society Institute. Stannary Hills Hospital. Boonah District Hospital.
SOUTH AUSTRALIAN: Secretary, 207, North Terrace, Adelaide.	All Contract Practice Appointments in South Australia. Booleroo Centre Medical Club.
WESTERN AUSTRALIAN: Honorary Secretary, 65, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.
NEW ZEALAND (WELLINGTON DIVISION): Honorary Secretary, Wellington.	Friendly Society Lodges, Wellington, New Zealand.

Medical practitioners are requested not to apply for appointments to position at the Hobart General Hospital, Tasmania, without first having communicated with the Editor of THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to "The Editor," THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, Sydney. (Telephones: MW 2651-2.)

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